Supreme Court, U.S.
FILED
134 (1) 09-117 JUL 24 2009
No.
OFFICE OF THE CLERK

In the Supreme Court of the United States

APOTEX, INC. and APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

ROBERT B. BREISBLATT
Katten Muchin Rosenman LLP
525 W. Monroe Street
Chicago, IL 60661
(312) 902-5200

ROBERT S. SILVER
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street 11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of record
ALAN E. UNTEREINER
DANIEL R. WALFISH
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W. Suite 411
Washington, D.C. 20006
(202) 775-4500

SHASHANK UPADHYE
Apotex, Inc.
150 Signet Drive
Toronto, ON M9L 1T9
Canada
(416) 401-7701

QUESTION PRESENTED

Under the Patent Act, "a patent may not be obtained" if its subject matter is "obvious" when judged in light of the prior art. 35 U.S.C. § 103. In *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007), this Court addressed several "fundamental misunderstandings" in the Federal Circuit's long-standing approach to this nonobviousness requirement, including its mistaken view that "a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'" *Id.* at 421-422. In this case, the Federal Circuit, without even acknowledging that admonition, held that a chemical substance, once isolated, was nonobvious without any regard to "whether . . . it may have been 'obvious to try'" isolating the substance. App., *infra*, 27a. Its rationale was that certain properties of the isolated substance were not predictable. The question presented is:

> Whether, if an experiment was "obvious to try," a *prima facie* case of obviousness is automatically rebutted by a showing that the outcome of the experiment was not entirely predictable.

RULE 29.6 STATEMENT

The ultimate parent of petitioners Apotex, Inc. and Apotex Corp. is Sherfam Inc., which is not publicly traded. No publicly traded company owns 10% of the shares of petitioners or of any of their parent corporations.

TABLE OF CONTENTS

Page

QUESTION PRESENTED i

RULE 29.6 STATEMENT ii

TABLE OF AUTHORITIES v

OPINIONS BELOW 1

JURISDICTION 1

STATUTORY PROVISION INVOLVED 1

STATEMENT 1

A. Background Principles 3

B. The Patents Covering Plavix 5

C. The District Court Proceedings 7

D. The Court of Appeals' Decision 9

REASONS FOR GRANTING THE PETITION 11

I. The Court of Appeals Has Failed To Heed This Court's Admonition That "Obvious To Try" *Can* Render an Invention Obvious 12

II. The Question Presented Arises Constantly and Is Tremendously Important 22

CONCLUSION 25

TABLE OF CONTENTS – cont'd

Page

APPENDIX A—Court of Appeals Opinion 1a

APPENDIX B—District Court Opinion 31a

APPENDIX C—Order Denying Rehearing 125a

Pursuant to Supreme Court Rule 33(1)(c), petitioners have separately duplicated certain patent documents in a Supplemental Appendix.

TABLE OF AUTHORITIES

Page(s)

Cases

Abbott Labs. v. *Sandoz, Inc.*,
544 F.3d 1341 (Fed. Cir. 2008)..... 20, 24

Alza Corp. v. *Mylan Labs., Inc.*,
464 F.3d 1286 (Fed. Cir. 2006)..... 18, 24

Ansonia Brass & Copper Co. v. *Elec. Supply Co.*,
144 U.S. 11 (1892) 14-15

Aventis Pharma Deutschland GmbH v. *Lupin, Ltd.*,
499 F.3d 1293 (Fed. Cir. 2007)..... 24, 25

Bonito Boats, Inc. v. *Thunder Craft Boats, Inc.*,
489 U.S. 141 (1989) 16

Compton v. *Metal Prods., Inc.*,
453 F.2d 38 (4th Cir.),
cert. denied, 406 U.S. 968 (1972) 15, 21

Emory Univ. v. *Glaxo Wellcome Inc.*,
44 U.S.P.Q.2d 1407 (N.D. Ga. 1997)..... 25

Feist Publ'ns, Inc. v. *Rural Tel. Serv. Co.*,
499 U.S. 340 (1991) 21

Forest Labs., Inc. v. *Ivax Pharms., Inc.*,
501 F.3d 1263 (Fed. Cir. 2007)..... 25

Gen. Elec. Co. v. *Jewel Incandescent Lamp Co.*,
326 U.S. 242 (1945) 14

TABLE OF AUTHORITIES – cont'd

Page(s)

Graham v. *John Deere Co.*,
383 U.S. 1 (1966) 8

In re Kubin,
561 F.3d 1351 (Fed. Cir. 2009)..... 19

KSR Int'l Co. v. *Teleflex Inc.*,
550 U.S. 398 (2007) .....*passim*

Ortho-McNeil Pharm., Inc. v. *Mylan Labs., Inc.*,
348 F. Supp. 2d 713 (N.D.W. Va. 2004)..... 25

Pfaff v. *Wells Elecs., Inc.*,
525 U.S. 55 (1998) 16

Pfizer, Inc. v. *Apotex, Inc.*,
480 F.3d 1348, rehearing denied,
488 F.3d 1377, cert. denied,
128 S. Ct. 110 (2007) 7, 18, 19, 23, 24

Pfizer Inc. v. *Ranbaxy Labs. Ltd.*,
405 F. Supp. 2d 495 (D. Del. 2005) 25

Procter & Gamble Co. v. *Teva Pharms. USA, Inc.*,
566 F.3d 989 (Fed. Cir. 2009)..... 24

Takeda Chem. Indus., Ltd. v. *Alphapharm Pty., Ltd.*,
492 F.3d 1350 (Fed Cir.),
cert. denied, 128 S. Ct. 1739 (2008)..... 20, 24

Univ. of Ill. Found v. *Winegard Co.*,
402 F.2d 125 (8th Cir.),
cert. denied, 406 U.S. 968 (1972)..... 15

TABLE OF AUTHORITIES – cont'd

Page(s)

Statutes

35 U.S.C. § 101 22

35 U.S.C. § 103 ..... 1, 21

35 U.S.C. § 154 7

35 U.S.C. § 156 7

35 U.S.C. § 271 7-8

Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585 (1984) 7

Other Authorities

BROWN, ORGANIC CHEMISTRY (1995) 3, 4, 5

Brown & Davies, *Chemical Asymmetric Synthesis*, 342 NATURE 631 (1989) 4

CHISUM ON PATENTS § 5.04 ..... 22, 23

Darrow, *The Patentability of Enatiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2 (2007) 23, 24

GRESSMAN ET AL., SUPREME COURT PRACTICE (9th ed. 2007) 11

TABLE OF AUTHORITIES – cont'd

Page(s)

Kitch, *The Nature and Function of the Patent System*, 20 J. L. & ECON. 265 (1977) 22

"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?, 76 FORDHAM L. REV. 2625 (2008) 5, 7, 23

PTO, *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court decision in* KSR International Co. v. Teleflex Inc., 72 FED. REG. 57526 (2007) 18, 19

Putting the Brakes on Drugs: The Impact of KSR v. Teleflex on Pharmaceutical Patenting Strategies, 42 GA. L. REV. 905 (2008) 23

Silverman, *The Schizophrenic Career of a "Monster Drug,"* 110 PEDIATRICS 404 (2002) 4

WERMUTH & STAHL, INTRODUCTION TO HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE (2002) 5

PETITION FOR A WRIT OF CERTIORARI

OPINIONS BELOW

The opinion of the Federal Circuit (App., *infra*, 1a-30a) is reported at 550 F.3d 1075. The district court's opinion (App., *infra*, 31a-124a) is reported at 492 F. Supp. 2d 353.

JURISDICTION

The judgment of the court of appeals was entered on December 12, 2008. App., *infra*, 1a. On March 26, 2009, the court of appeals denied a timely petition for panel rehearing and rehearing en banc. App., *infra*, 125a-126a. On May 29, 2009, the Chief Justice extended the time to petition for a writ of certiorari to and including July 24, 2009. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Section 103 of Title 35 of the United States Code provides, in pertinent part:

> (a) A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT

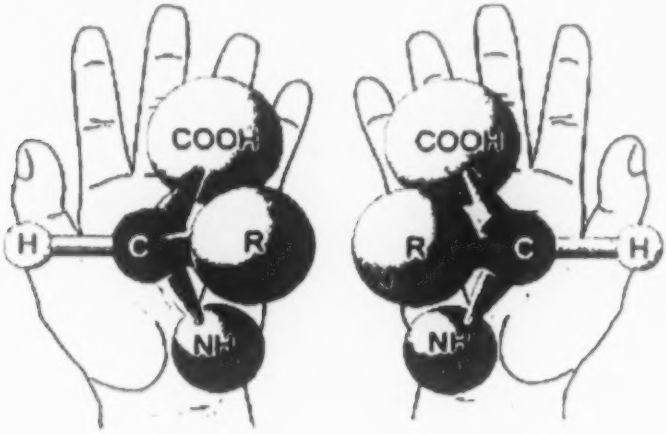
The question presented in this case arises

constantly in patent litigation. If an experiment is prompted by common knowledge in a field but its results cannot be predicted until the experiment is performed, does patentability turn on the *outcome* of the experiment, or is the inquiry rather whether the experiment was "obvious to try" in the first place? *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007), supplies a clear answer to this question, and yet the Federal Circuit addresses it in different ways depending on the particular three-judge panel that happens to hear a case. That confusion is entrenched; the Federal Circuit has repeatedly declined to review this issue en banc.

In this case, respondents (collectively "Sanofi") already had a patent on a substance that had shown promise as an anti-blood-clotting agent (*i.e.*, a blood thinner) and that was known to be a mixture of two closely related molecules. After obtaining that patent – which covered not just the mixture but each of the two constituent molecules – Sanofi isolated the two constituents, and found that one had especially pronounced anti-blood-clotting effects, whereas the other was inactive or toxic. Sanofi then obtained an additional patent that covered only the beneficial molecule in isolation. That molecule became the basis of the blockbuster blood-thinning drug Plavix. Plavix, however, was also protected by the first patent, which by itself gave Sanofi many highly profitable years of market exclusivity. The second patent's only function has been to prolong Sanofi's monopoly by eight years, and the question is whether the Federal Circuit correctly analyzed the validity of that patent.

A. Background Principles

Many organic molecules, including many drugs, exist in two forms that are exact mirror images. The two are alike in every way except for their spatial orientation: as with the left and right hand, the forms cannot be superimposed on each other. (This type of spatial asymmetry is known as "chirality." Many everyday objects, such as screws and airplane propellers, are chiral.) The two forms of such a molecule are called enantiomers, and can be described (depending on the direction in which they rotate polarized light) as either "left-handed" (or "levorotatory") or "right-handed" (or "dextro-rotatory"). *E.g.*, WILLIAM H. BROWN, ORGANIC CHEMISTRY 266-268, 278-279 (1995); App., *infra*, 8a. Here, for example, is a schematic illustration of the "handedness" of the enantiomers of a simple amino acid structure:



A substance consisting of an equal mixture of two enantiomers is called a "racemic" mixture, or a "racemate." *E.g.*, App., *infra*, 8a. The parties dispute whether, given a patent on a racemic mixture and its

constituent enantiomers, a later patent on only one of the enantiomers in isolation was obvious.

Enantiomers of the same molecule can have dramatically different biological effects. A notorious example is thalidomide, a tranquilizer that was marketed around the world from 1957 to 1961. *E.g.*, William A. Silverman, *The Schizophrenic Career of a "Monster Drug,"* 110 PEDIATRICS 404, 405-406 (2002). Thalidomide is a racemate, but it is believed that only the left-handed enantiomer is responsible for the sedative effects, whereas the right-handed twin produces birth defects. *E.g.*, John M. Brown & Stephen G. Davies, *Chemical Asymmetric Synthesis*, 342 NATURE 631, 631 (1989). Such "stereoselectivity" is common (if not usually so disastrous) in the world of organic chemistry and has been recognized by chemists for decades. See App., *infra*, 56a. "For racemic drugs, most often only one enantiomer exerts the beneficial effect, whereas the other enantiomer either has no effect, or exerts a detrimental effect. Thus, enantiomerically pure drugs should, more often than not, be more effective than their racemic counterparts." BROWN, *supra*, at 300.

For this reason, in February 1987 the U.S. Food and Drug Administration, following discussions with industry representatives, advised that sponsors of a new drug substance should "have either separated the various potential" enantiomers of the substance "or synthesized them independently." C.A. App. 17548. The agency also noted that individual enantiomers "may need to be studied for pharmacological and toxicological properties (and/or for safety and efficacy)." *Ibid.* Given these scientific and regulatory realities, "many drug companies have decided to

develop only single enantiomers of new chiral drugs." BROWN, *supra*, at 300.

B. The Patents Covering Plavix

Sanofi was no exception. On July 16, 1985, Sanofi was granted a patent on a substance known as PCR4099 and its chemical relatives, which were found to inhibit the aggregation of blood platelets. App., *infra*, 47a; Supp. App. S1, S3 col. 3 ll. 36-57; Supp. App. S12. The patent (U.S. Patent No. 4,529,596, or "the '596 patent") and its foreign counterparts (together, the "Aubert patents") acknowledged that PCR4099 and its relatives are chiral molecules that may exist in the form of two enantiomers, and claimed not only "both enantiomeric forms" of these compounds but also "their mixture." *E.g.*, Supp. App. S2 col. 1 ll. 38-41, S8 col. 13 ll. 17-18. The Aubert patents also claimed PCR4099's (and its enantiomers') "salts [formed from] pharmaceutically acceptable . . . acids." *Id.* at S8 col. 13 ll. 8-10; see also Supp. App. S23.[1]

Although the Aubert patents potentially covered a large number of chemical substances, it was clear that PCR4099 in particular merited further attention. The patents used it as their lead example of the class of molecules, and reported the results of

---

[1] Drugs are commonly administered in the form of a "salt," which in chemical parlance refers to the product of a reaction between an acid and a base. Where, as here, the drug in question is a base, a pharmaceutical salt is formed by reacting it with an acid. See, e.g., Note, *"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625, 2649 n.164 (2008) (citing WERMUTH & STAHL, INTRODUCTION TO HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE 1 (2002)).

tests in which PCR4099 exhibited very favorable anti-clotting activity. *E.g.*, Supp. App. S6-S7. In July of 1985, Sanofi promoted PCR4099 (but no other compound covered by the Aubert patents) in a paper and at a conference. App., *infra*, 54a. It was common knowledge, however, that drugs that appeared safe could exhibit serious side effects once on the market. *Id.* at 55a. And, as explained above, workers in the industry had strong reasons to try to separate chiral drugs into their enantiomers.

Accordingly, only a few months after obtaining the '596 patent, Sanofi's researchers in November 1985 asked a staff chemist to separate PCR4099 into its constituent enantiomers (which, as noted above, were covered by the Aubert patents). App., *infra*, 9a. He used a technique, known as "diastereomeric salt formation," that originated with Louis Pasteur in the 19th century. *Id.* at 10a. Testing revealed that the dextrorotatory ("right-handed") enantiomer was a highly effective anti-clotting agent whereas the levorotatory ("left-handed") twin had no such effects. At the same time, the left-handed enantiomer was far more toxic than the right-handed twin. *Ibid.* The right-handed enantiomer became known as "clopidogrel," and Sanofi applied for a separate U.S. patent on isolated clopidogrel plus its pharmaceutically acceptable salts. The patent issued on July 11, 1989, as No. 4,847,265 ("the '265 patent"). Supp. App. S29. Sanofi also determined that clopidogrel could be packaged and administered in the form of a bisulfate salt, known as clopidogrel bisulfate.[2] App.,

---

[2] As explained in note 1 above, a salt is formed by reacting the drug with an acid. There is nothing particularly remarkable about this process, which is a "common practice in the

infra, 11a. Claim 3 of the '265 patent specifically recites this compound.

In 1997, the FDA approved the sale of clopidogrel bisulfate, which Sanofi exclusively markets as Plavix. App., *infra*, 32a. Plavix is routinely prescribed to treat or prevent heart attacks, strokes, and other cardiovascular events. The '596 patent expired in 2003, *id.* at 34a, but the '265 patent term lasts until 2011, *id.* at 33a.[3]

C. The District Court Proceedings

Petitioners (collectively "Apotex") manufacture and distribute generic drugs. In November 2001, Apotex applied under the Hatch-Waxman Act[4] for FDA approval to market clopidogrel bisulfate following the expiration of the '596 patent (whose validity is undisputed). Sanofi then sued for infringement of the '265 patent, see 35 U.S.C.

---

pharmaceutical industry." Note, *"Obvious to Try"*, *supra* note 1, at 2649 n.164; see also *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, 1353 (Fed. Cir. 2007) ("Active drug molecules . . . are frequently made into pharmaceutically-acceptable acid addition salts to improve their bioavailability."). The FDA has approved a finite set of acids for this purpose. See, *e.g.*, App., *infra*, 73a. The bisulfate (also known as hydrogen sulfate) salt is obtained by reacting the drug with sulfuric acid, which is on the list of FDA-approved acids and was one of the first acids that Sanofi tested. *Id.* at 74a.

[3] That term is 20 years from the date of application (in this case February 12, 1988), see 35 U.S.C. § 154(c)(1), plus an extension to compensate for the FDA review period. See *id.* § 156.

[4] The Act (officially named the Drug Price Competition and Patent Term Restoration Act of 1984) governs the system of generic drugs. Among other things, the Act facilitates challenges to the validity of drug patents. See Pub. L. 98-417, 98 Stat. 1585 (1984).

§ 271(e)(2)(A), and Apotex counterclaimed for a declaration that the patent is invalid. App., *infra*, 3a. The district court held a bench trial, and ruled on June 19, 2007.

Confronting Apotex's obviousness challenge, Judge Stein observed that *Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966), instructs a court to assess obviousness principally with reference to: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art. App., *infra*, 102a-103a. Judge Stein then assumed that Apotex had made out a *prima facie* case of obviousness given the prior disclosure of PCR4099 together with "the prior art teachings that (1) racemic compounds may be separated into their enantiomers; and (2) those enantiomers . . . may exhibit different biological activity or different degrees of the same type of biological activity exhibited by the racemate." *Id.* at 106a-107a.

The district court, however, believed that "it is not enough for Apotex to have shown that the [elements] found in Claim 3 of the '265 patent would have been 'obvious to try.'" App., *infra*, 103a. Relying on a series of Federal Circuit cases that antedated *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (Apr. 30, 2007) – and without even citing *KSR* – the district court reasoned that "evidence of the fact that *any* property of clopidogrel bisulfate is unexpected as compared to PCR4099 or anything else in the prior art rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate." App., *infra*, 107a (emphasis added). That condition, the court added, was satisfied here because the precise properties of

the two enantiomers as compared with each other and the racemate could not have been "predict[ed] with a reasonable expectation of success." *Ibid.* The '265 patent accordingly was nonobvious, and this was true "[w]hether or not it may have been 'obvious to try' separating the enantiomers of PCR4099 and, secondarily, preparing its dextrorotary enantiomer as a bisulfate salt." *Id.* at 112a. The district court entered judgment in favor of Sanofi. *Id.* at 124a.

D. The Court of Appeals' Decision

The Federal Circuit affirmed. It agreed with the district court that clopidogrel bisulfate was nonobvious regardless of whether the compound was "obvious to try," see App., *infra*, 27a, endorsed the district court's focus on "the unpredictable and unusual properties of the dextrorotatory enantiomer," *id.* at 21a, and rejected Apotex's argument that "the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties," *id.* at 27a-28a.

The Federal Circuit highlighted testimony to the effect that "the therapeutic and toxic properties of the enantiomers" could not be predicted in advance, that "it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested"; and that so-called "absolute stereoselectivity" (the two enantiomers of the same molecule having completely different biological effects) "is rare." App., *infra*, 23a. On this basis, the Federal Circuit upheld the district court's finding "that a person of ordinary skill in this field would not

reasonably have predicted that the dextrorotatory enantiomer [of PCR4099] would provide all of the [therapeutic] activity and none of the adverse neurotoxicity." *Id.* at 24a.

The Federal Circuit also reached beyond the reasons that the district court gave for holding the patent nonobvious (see App., *infra*, 104a-112a), pointing to the "difficulty" of the enantiomeric separation, and the time and effort needed to perform it. App., *infra*, 25a-26a. And the Federal Circuit agreed with the district court that "Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR4099, before [deciding to try] separating the enantiomers, also weighed against finding that separation would have been obvious," *id.* at 26a; App., *infra*, 108a.

The Federal Circuit also thought that rendering clopidogrel as the bisulfate salt was not obvious because the scientific literature listed many acids "as candidates for forming salts with basic drug compounds," and the parties' experts agreed that it was "unpredictable" whether any "particular acid-base combination" would yield a pharmaceutically suitable salt. App., *infra*, 27a. Finally, the Federal Circuit agreed with Sanofi that *KSR*'s lessons were inapplicable insofar as this case involved a procedure with an unpredictable result rather than a mechanical combination of familiar elements "having the properties of the known components." *Id.* at 29a-30a.

The Federal Circuit denied Apotex's petition for rehearing en banc. App., *infra*, 126a.

REASONS FOR GRANTING THE PETITION

The question presented arises constantly in many industries and has enormous economic importance. In many fields of science and other useful arts, experimenters using known methods frequently do not know how a particular substance or product will behave before they create it. Yet if, as the Federal Circuit's holding would have it, any new compound with at least some unpredictable properties is nonobvious, then nearly *every* new substance would qualify for a patent, and the patent system would "stifle, rather than promote, the progress of useful arts." *KSR Int'l Co.* v. *Teleflex Inc.*, 550 U.S. 398, 427 (2007).

KSR explained that a finding that an approach is "obvious to try" might well suffice to render the resulting invention obvious. The U.S. Patent and Trademark Office has followed suit. But the Federal Circuit has failed to apply that lesson consistently despite repeated unsuccessful requests for rehearing en banc and dissents by some of the court's members. This entrenched confusion harms brand-name product developers and would-be generic competitors; both types of companies make decisions about which products to develop and market based on standards of patentability.

Certworthiness of a Federal Circuit decision is often "found in the Federal Circuit's treatment of patentability standards, or in its treatment of an exceptionally significant patent, or in its application of Supreme Court precedent." EUGENE GRESSMAN ET AL., SUPREME COURT PRACTICE 287 (9th ed. 2007); see also *KSR*, 550 U.S. at 407 ("Because the Court of Appeals addressed the question of obviousness in a

manner contrary to § 103 and our precedents, we granted certiorari."). This case presents every one of those circumstances, and more. This Court should grant review, resolve the confusion in the Federal Circuit's case law, and clarify that *KSR* applies even when certain aspects of the art are inherently unpredictable.

I. The Court of Appeals Has Failed To Heed This Court's Admonition That "Obvious To Try" *Can* Render an Invention Obvious

A. *KSR* explicitly rejected the analysis used below. In *KSR*, the Federal Circuit had deployed a series of doctrines to avoid concluding that a patent was obvious, even though the invention – titled "Adjustable Pedal Assembly With Electronic Throttle Control" – was just a mechanical combination of two already well-known components. See 550 U.S. at 406, 413-415. The Federal Circuit thought it irrelevant "[t]hat it might have been obvious to try the combination of [an adjustable pedal assembly] and [an electronic] sensor," because, according to the Federal Circuit, "'obvious to try' has long been held not to constitute obviousness." *Id.* at 414 (internal quotation marks omitted).

This Court disagreed:

> [T]he Court of Appeals . . . conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill

> has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421 (citation omitted).

The district court and the Federal Circuit flatly ignored this teaching. (The district court ruling did not even cite *KSR*, which antedated the ruling by two months.) See App., *infra*, 103a (quoting Federal Circuit: "We have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103."); App., *infra*, 27a (agreeing that the '265 patent was nonobvious "[w]hether or not it may have been 'obvious to try' preparing clopidogrel bisulfate"). Apotex, however, was entitled to have the courts below ask the questions posed by this Court in *KSR*: whether there was a "design need" or other "pressure" to solve a problem (namely, the isolation of the enantiomers of a promising racemate and the preparation of a pharmaceutically acceptable salt) and a "finite number of identified, predictable solutions" (namely, the reagents and concentrations that one varies in order to separate enantiomers and prepare a pharmaceutical salt) such that Sanofi's workers had good reason "to pursue the known options within [their] technical grasp." Had the courts below asked those crucial questions mandated by *KSR*, they might have recognized that Sanofi's successful enantiomeric separation and salt formation was "the product not of innovation but of ordinary skill and common sense."

B. Instead, the courts below focused on the *outcome* of Sanofi's experiments, and in particular on whether any aspect of that outcome was unexpected. See App., *infra*, 107a ("[E]vidence of the fact that *any* property of clopidogrel bisulfate is unexpected . . . rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate." (emphasis added)). Yet both sides agree that it was known that the properties (both therapeutic and toxic) of enantiomers often differ, even if the exact nature and degree of difference could not have been known. And it is undisputed that the properties of a racemate are the sum of the properties of its enantiomers. Thus, given a known racemate, the only unknown will be the precise *allocation* of its properties to the enantiomers.[5] In hanging patentability on this "known unknown," the Federal Circuit essentially said that any element of unpredictability or unexpectedness in an experiment suffices to patent the result.

That fixation on unexpectedness or unpredictability has no support in, and in fact clashes with, this Court's decisions. When "the prior art discloses the method of making an article having the characteristics of the patented product," this Court has noted, the patent is invalid, "[even] though all the advantageous properties of the product had not been fully appreciated." *Gen. Elec. Co.* v. *Jewel Incandescent Lamp Co.*, 326 U.S. 242, 248 (1945). In fact, by the end of the 19th century, "nothing [wa]s better settled in this [C]ourt than that the application of an old process to a new and analogous purpose does not

---

[5] The testing required to determine those properties once the enantiomers are isolated is routine (if time-consuming), and nobody has suggested otherwise.

involve invention, *even if the new result had not before been contemplated*." *Ansonia Brass & Copper Co.* v. *Elec. Supply Co.*, 144 U.S. 11, 18 (1892) (emphasis added).

This point was appreciated by at least some of the courts of appeals before the Federal Circuit was created. See *Univ. of Ill. Found.* v. *Winegard Co.*, 402 F.2d 125, 127 (8th Cir.) ("The statutory standard of patentability under § 103 is not 'predictability.' . . . Where logical exploration within known principles of the science achieves an unpredictable result, even though a commercially desirable one, the burden of nonobviousness is not necessarily overcome."), cert. denied, 394 U.S. 917 (1969); *Compton* v. *Metal Prods., Inc.*, 453 F.2d 38, 42 (4th Cir.) ("'The ultimate question is whether a hypothetical person having ordinary skill in the art would have readily found the same solution when addressing himself to the same problem.'"), cert. denied, 406 U.S. 968 (1972). Having been rebuffed in *KSR* for according too little weight to the fact that a new approach was "obvious to try," the Federal Circuit has resurrected long-discarded notions to try to rebut the inference that arises from the obviousness of trying a particular approach.

What is more, the Federal Circuit's approach is fundamentally inconsistent with one of *KSR*'s core animating principles: "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 550 U.S. at 419. The whole reason for the nonobviousness requirement is that the patent system is supposed to reward not (as the decisions below seem to have assumed) every single incremental advance, but rather *only advances that would have been less likely*

without the promise of a patent. The "carefully crafted bargain" embodied in the patent system confers exclusive rights for a period of years only as a means to "the ultimate goal" of "bring[ing] new designs and technologies *into the public domain.*" *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-151 (1989) (emphasis added); accord *Pfaff* v. *Wells Elecs., Inc.*, 525 U.S. 55, 63-64 (1998). If an invention was going to enter the public domain anyway, then almost by definition a separate patent on it only "retards progress."

The right-handed enantiomer of PCR4099 turned out to be a better drug than the racemic mixture, but there are excellent reasons to believe that Sanofi would have separated PCR4099 into its components (and then selected an appropriate salt) "in the ordinary course." (Those reasons include PCR4099's known properties as a blood thinner, and the potential benefits of separating a racemic mixture into its constituent enantiomers.) And if no additional inducement was needed for this incremental advance, then additional exclusivity cannot possibly promote the purposes of the patent system.

In fact, it is telling that Sanofi would have been rewarded handsomely for its investments even without the later '265 patent. The earlier '596 patent gave Sanofi 20 years of exclusive rights in the United States to PCR4099 and its component enantiomers. That period expired only after Plavix had been on the market for five or six years as one of the world's top-selling drugs – and could have lasted even longer if Sanofi had relied only on the '596 patent to protect Plavix. See note 3, *supra*. Conferring an additional eight years of exclusivity through the '265 patent, see

page 7 *supra*, is an abuse of the patent system's "carefully crafted bargain" – it has postponed competition in the market for an important drug with no corresponding societal benefit.

In sum, the Federal Circuit was quite wrong to distinguish *KSR* on the ground that it involved a mechanistic combination of known components rather than a chemical refinement with a not-fully-predictable result. The basic lesson of *KSR* is that not every incremental advance should qualify for twenty years of exclusivity. That lesson is not limited to mechanical engineering, nor is it any less applicable simply because some aspects of a technology are inherently unpredictable.

C. The approach adopted below runs counter to that of the PTO and contributes to incoherence in the Federal Circuit's case law. Following *KSR*, the PTO issued new examination guidelines for determining obviousness. The guidelines, which cite and closely track *KSR*, are wholly inconsistent with the analysis employed by the courts below. They direct a patent examiner to reject claims as "Obvious To Try" if he or she finds:

> (1) . . . that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) . . . that there had been a finite number of identified, predictable solutions to the recognized need or problem;
>
> (3) . . . that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

> (4) whatever additional findings based on the *Graham* factual inquiries [(see page 8, *supra*)] may be necessary . . . to explain a conclusion of obviousness.

PTO, *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of [KSR]*, 72 FED. REG. 57526, 57529, 57532 (2007).

As "Example 1" of this analysis, the guidelines discuss *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir.), cert. denied, 128 S. Ct. 110 (2007). In that case, the patentee had argued that the results of forming a particular pharmaceutical salt "would have been unpredictable, and therefore were nonobvious." 75 FED. REG. at 57532. The panel, however, "*rejected the notion that unpredictability could be equated with nonobviousness* here, because there were only a finite number (53) of pharmaceutically acceptable salts to be tested." *Ibid.* (emphasis added). In other words, a degree of unpredictability does not overcome "obvious to try."[6]

---

[6] Similarly, the PTO uses as "Example 2" of "Obvious To Try" another Federal Circuit case in which, according to the PTO, "it would have been obvious to try the known methods . . . , with a reasonable expectation of success. The court was not swayed by arguments of a lack of absolute predictability." *Ibid.* (citing *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286 (2006)). Both *Pfizer* and *Alza* were decided between the *KSR* cert. grant and opinion, at a time when Federal Circuit judges had made no secret of their apprehension of a potential reversal in *KSR*. See 550 U.S. at 421 ("We note the [Federal Circuit] has since elaborated a broader conception of [its obviousness] test than was applied in the instant matter." (citing *Alza*)). The PTO's third and final example of "Obvious to Try" was *Ex Parte Kubin*, a PTO administrative appeal since affirmed by the Federal Circuit. The *Kubin* decisions closely track *KSR*'s discussion of "obvious

As if to provide a neat demonstration of the inconsistency in the Federal Circuit's obviousness jurisprudence, in the present case, three different Federal Circuit judges reached the opposite conclusion from the *Pfizer* panel about the obviousness of the salt formation, even though Sanofi had merely chosen from among *the exact same list of 53 acids* at issue in *Pfizer*. See, *e.g.*, App., *infra*, 70a, 73a; see also note 2, *supra*. The difference between the two cases is explained not by their facts (which as regards salt formation were quite similar), but by the legal analysis. The panel in this case relied on what the *Pfizer* panel and the PTO have disclaimed: the unpredictability of the chemical reactions. What is more, three of the Federal Circuit's judges wanted the court to rehear *Pfizer* en banc. They criticized *Pfizer*'s use of an "obvious to try" analysis (even though by then *KSR* had endorsed it) and emphasized the supposedly "unexpected properties" of the patented substance. See 488 F.3d 1377, 1379-1384 (2007). Two of those dissenting three judges were panelists in this case.

Those judges' views have tended to prevail in other cases as well. For example, the author of the opinion below decided in another recent case that a patented drug delivery formulation was likely not "obvious to try" under *KSR*, even though it was within a finite universe of known options suggested

---

to try," see 72 FED. REG. at 57532; *In re Kubin*, 561 F.3d 1351, 1358-1361 (Fed. Cir. 2009), but *Kubin* does not present the question whether a showing of any unpredictability negates obviousness based on "obvious to try." See 561 F.3d at 1360 ("[T]his record shows that one of skill in this advanced art would find these claimed 'results' profoundly 'predictable.'").

by the prior art, because "the results obtainable from" any one "selected component" were not predictable. *Abbott Labs.* v. *Sandoz, Inc.*, 544 F.3d 1341, 1350-1351 (Fed. Cir.), reh'g denied (Feb. 23, 2009).[7] And a panel led by another of the judges who decided the present case approved a district court's pre-*KSR* dictum to the effect that "unexpected results" could rebut a *prima facie* case of obviousness. See *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1354, 1359, 1360-1362 (Fed. Cir.), reh'g denied (Sept. 27, 2007), cert. denied, 128 S. Ct. 1739 (2008).

Thus while at least one Federal Circuit panel (and the PTO) have focused correctly on the obviousness of the path followed to reach a result, most of the others have focused on whether the properties of the result could have been precisely predicted in advance, implicitly assuming that *KSR* does not apply when there is such unpredictability. The approach seems to depend in large part on who the panelists are. And yet the Federal Circuit (in stark contrast to the PTO) is making no effort to harmonize its rulings with each other and with *KSR*.

The result is enormous uncertainty in an area of the law in which certainty is crucial. Companies make research, development, investment, and marketing decisions based on predictions about whether potential inventions will qualify for patents in the PTO, and whether issued patents will survive court

---

[7] This rationale was advanced by Judge Newman's "Opinion for the court," *id.* at 1343. One judge dissented. See *id.* at 1378. The third concurred in the judgment, but without joining this section of the opinion or authoring another.

challenges. When the Federal Circuit's behavior is not only inconsistent but regularly in conflict with that of the PTO, it becomes impossible to make reliable predictions. This kind of uncertainty is extraordinarily harmful to consumers as well as companies. For example, in the pharmaceutical industry, such uncertainty emboldens brand companies to seek to enforce questionable patents and deters potential competitors from challenging those efforts.

D. The Federal Circuit's subsidiary justifications for upholding the patent – namely that Sanofi had spent tens of millions of dollars on developing the racemate *before* deciding to separate the enantiomers, and that separating the enantiomers was time- and labor-intensive, see page 10, *supra* – are also misplaced and will work great mischief if left in place. First of all, "sweat of the brow" is not a criterion for patentability. See 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made."); *Compton*, 453 F.2d at 42 ("Neither is the amount of time spent by Compton in devising the method a controlling factor."); cf. *Feist Publ'ns, Inc.* v. *Rural Tel. Serv. Co.*, 499 U.S. 340, 359-360 (1991). Were it otherwise, many laborious but unimaginative undertakings that would "occur in the ordinary course" and do not represent "real innovation," 550 U.S. at 419, would qualify for a patent.

What is more, the investment that impressed the lower courts mostly took place *before* the Aubert patents and Sanofi's public promotion of PCR4099 – the very prior art disclosures against which the later patent must be judged. Sanofi's investment, in other words, was protected by – and rewarded with – the

earlier patents. To reward Sanofi for its *earlier* investment by upholding a *later* patent on an inexorable minor advance is to violate the patent bargain in precisely the way that *KSR* warned against.[8]

II. The Question Presented Arises Constantly and Is Tremendously Important

The patent statute covers (among several other categories of invention) "new and useful . . . composition[s] of matter." 35 U.S.C. § 101. But it is rarely if ever possible to know all of the properties of a new composition of matter before it is created. See, *e.g.*, CHISUM ON PATENTS § 5.04[6], at 5-472 (2008) ("Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties."). In fields devoted to generating new compositions of matter, workers of ordinary skill conduct experiments every day in the belief that they are reasonably likely to obtain a useful result – even though they cannot

---

[8] Contrary to what the Federal Circuit apparently assumed, it is not at all clear that a patent should be available as the end product of any successful research and development work. An influential academic account offers the insight that a patent is designed to claim a space in which, for a limited time, the patentee alone has the right to "prospect" by developing "known technological possibilit[ies]" within that space. Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J. L. & ECON. 265, 266 (1977). A patent, in other words, can be seen as an initial condition for, not the culmination of, a research and development effort. The '596 patent appropriately ensured that only Sanofi could work with PCR4099, but that does not mean that all of the additional work Sanofi did with PCR4099 in turn should qualify for a new patent.

perfectly predict what the result will be. If any degree of unpredictability or unexpectedness sufficed to impart patentability, then virtually every new substance could be removed from the public domain for at least 20 years, even when creating or isolating it was the obvious thing to do.

Accordingly, the question presented – which the leading treatise describes as a "key problem" in patent law, CHISUM, *supra*, § 5.04[6], at 5-472 – is critical to the public's ability to access the fruits of fields like pharmacology, biotechnology, industrial and agricultural chemistry, and the like. See, *e.g.*, *Pfizer*, 480 F.3d at 1367 (recognizing potential impact on the pharmaceutical industry of an obviousness standard based on "obvious to try"); Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, 3 & n.20 (2007) (noting significance to chemical industries generally of patentability of chiral molecules); Note, *Putting the Brakes on Drugs: The Impact of KSR v. Teleflex on Pharmaceutical Patenting Strategies*, 42 GA. L. REV. 905 (2008); Note, *"Obvious To Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625 (2008). The decision below, and others like it, create an incentive to game the system by engaging in what might be called the inventing of patents rather than the patenting of inventions. And when, as in this case and many others, the product with the supposedly "unpredicted" features is in a category to which one already has exclusive rights, the only effect of the additional patent is gratuitously to extend a monopoly that was supposed to be of limited duration.

This phenomenon is of particular concern in the pharmaceutical industry, because it allows companies with patents on brand-name drugs to delay consumers' access to generic drugs, which not only are themselves cheaper but also provide competition that often reduces the prices of brand-name drugs. Limiting competition in turn has adverse effects on the overall cost and availability of heath care. There will always be new methods of modifying drugs or isolating promising variants, and it will never be possible to predict all of the properties of a new substance. The Federal Circuit's decision, by providing a roadmap for pharmaceutical patent-holders seeking to extend monopolies that no longer serve any social purpose, contributes to the needless escalation of already soaring health-care costs.

Cases presenting this issue abound. In the past three years alone, the Federal Circuit has issued published – but inconsistent – decisions in at least seven such cases.[9] Moreover, the specific fact pattern presented here (an enantiomer patented over the racemic mixture) is a good vehicle for examining the issue. For one thing, it neatly illustrates the question presented. In fact, this is the paradigmatic (though far from only) context in which the question presented arises. See Darrow, *The Patentability of Enantiomers*, *supra*, at 37-51. And the pertinent scientific principles here are limited in number and

---

[9] In addition to this case, see *Abbott Labs.*, *supra*; *Takeda Chem.*, *supra*; *Pfizer*, *supra*; *Alza*, *supra*; *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293, 1301-1303 (Fed. Cir. 2007), reh'g denied (Dec. 3, 2007); *Procter & Gamble Co.* v. *Teva Pharms. USA, Inc.*, 566 F.3d 989, 994-998 (Fed. Cir. 2009).

relatively accessible, especially in comparison to other pharmacology and biotechnology cases.

Finally, litigation over this fact pattern has become quite common, giving this Court the benefit (especially valuable in a technical area) of reference points from other courts' reactions to similar cases. See, *e.g.*, *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007); *Forest Labs., Inc.* v. *Ivax Pharms., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007); *Pfizer Inc.* v. *Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 516-519 (D. Del. 2005); *Ortho-McNeil Pharm., Inc.* v. *Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 749-755 (N.D.W. Va. 2004); *Emory Univ.* v. *Glaxo Wellcome Inc.*, 44 U.S.P.Q.2d 1407, 1414 (N.D. Ga. 1997).

In sum, this Court should review an approach to patentability that will "stifle, rather than promote, the progress of useful arts," *KSR*, 550 U.S. at 427. Because the Federal Circuit has shown no interest in resolving the confusion in its cases, the perception of an appellate lottery on the question presented will endure until this Court speaks. This Court should clarify that *KSR*'s guidance is not limited to cases involving mechanical combinations, but applies even when there is an element of unpredictability to the technology. This is the right case in which to do so.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

ROBERT B. BREISBLATT
Katten Muchin Rosenman LLP
525 W. Monroe Street
Chicago, IL 60661
(312) 902-5200

ROBERT S. SILVER
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street
11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of record
ALAN E. UNTEREINER
DANIEL R. WALFISH
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W.
Suite 411
Washington, D.C. 20006
(202) 775-4500

SHASHANK UPADHYE
Apotex, Inc.
150 Signet Drive
Toronto, ON M9L 1T9
Canada
(416) 401-7701

JULY 2009

APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2007-1438

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs-Appellees,

v.

APOTEX, INC. and APOTEX CORP.,

Defendants-Appellants.

Appeal from the United States District Court for the Southern District of New York in case no. 02-CV-2255, Judge Sidney H. Stein.

DECIDED: December 12, 2008

Before NEWMAN, LOURIE, and BRYSON, *Circuit Judges*.

NEWMAN, *Circuit Judge*.

This suit arose in accordance with the provisions of the Hatch-Waxman Act, codified at 35 U.S.C. § 271(e) and 21 U.S.C. § 355(j). The patent at issue is

United States Patent no. 4,847,265 (the '265 patent), owned by Sanofi-Synthelabo and related companies (collectively "Sanofi"), and covers the pharmaceutical product having the common name clopidogrel bisulfate and the brand name Plavix®. The product has the property of inhibiting the aggregation of blood platelets, and is used to treat or prevent blood-thrombotic events such as heart attacks and strokes. We affirm the district court's ruling sustaining patent validity.

BACKGROUND

Clopidogrel is the common name of the dextro-rotatory isomer of the chemical compound named methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate. Claim 3 of the patent is in suit:

> 3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-)thienopyridyl)(2-chlorophenyl)-acetate sub-stantially separated from the levo-rotatory isomer.

The '265 patent was issued on July 11, 1989, with priority from an application first filed in France in 1987. Approval of the product by the United States Food and Drug Administration (FDA) was received in 1998.

Apotex, Inc. filed an Abbreviated New Drug Application (ANDA)[1] in November 2001 for FDA ap-

---

[1] Federal approval of a generic counterpart of a previously approved drug pursuant to an ANDA requires showing that the generic product is the same as the approved product; evidence

proval to sell clopidogrel bisulfate, stating, pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV), that it believed the '265 patent to be invalid. Such "paragraph IV certification" is defined as an act of infringement for litigation purposes, 35 U.S.C. §271(e), in order to facilitate pre-marketing legal challenge by the producer of a generic form of a patented pharmaceutical product. In accordance with the statutory procedures Sanofi duly filed suit for infringement, and Apotex counterclaimed that the '265 patent is invalid on several grounds and unenforceable. The suit initiated a thirty-month stay of FDA approval of Apotex's ANDA, as provided by 21 U.S.C. §355(j)(5)(B)(iii). A proposed settlement was not achieved, the statutory stay expired, the FDA approved the Apotex ANDA, and Apotex commenced sale of its generic clopidogrel bisulfate product on August 8, 2006. Sanofi then moved in the district court for a preliminary injunction, asking that Apotex be enjoined from marketing its infringing product while the litigation was pending, noting that infringement was conceded by Apotex.

The district court found that Sanofi was likely to succeed on the merits of the validity and enforceability of the '265 patent, and that the equitable factors of the balance of harms, the probability of irreparable harm, and the various public interests, favored granting the injunction. *Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 350 (S.D.N.Y. 2006) ("*Sanofi I*"). This court affirmed the district court's rulings, while explaining that the record on the

---

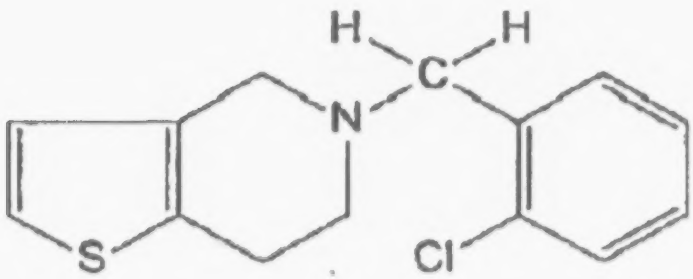
of safety and efficacy of the generic product is not required. *See* 21 U.S.C. §§ 355(j)(2)(A) and 355(b)(1).

substantive issues was necessarily incomplete and that the district court could review all aspects at trial. *See Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368, 1374-84 (Fed. Cir. 2006) ("*Sanofi II*") (holding that the patentee was likely to succeed on the merits, and that the balance of hardships and public interest supported the injunction). A bench trial was held from January 22 to February 15, 2007, following which the district court ruled that the '265 patent is valid and enforceable. *Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 397 (S.D.N.Y. 2007) ("*Sanofi III*").

This appeal is focused on the question of patentability of this dextrorotatory isomer in view of its known racemate described in earlier Sanofi patents, specifically, Sanofi's United States Patent No. 4,529,596 (the '596 patent) and Canadian Patent No. 1,194,875 (the '875 patent). Both reference patents are derived from the same French priority filing and are prior art against the '265 patent.

The activities that led to the product in suit are discussed in the earlier opinions, and are summarized as relevant herein: In 1972 Sanofi scientists were seeking products that might have improved anti-inflammatory properties, and in the course of this work discovered that certain compounds of the class known as thienopyridines (compounds having a thiene ring fused to a pyridine ring) have the property of inhibiting blood platelet aggregation. Sanofi scientists, led by Dr. Jean-Pierre Maffrand, pursued this direction of research. The record states that they initially synthesized and evaluated several hundred chemical modifications and derivatives of

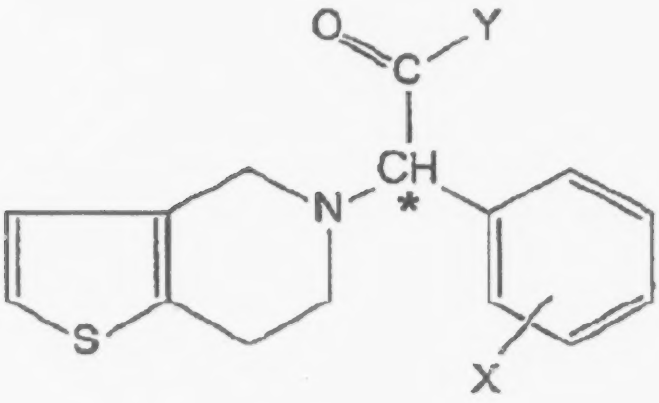
thienopyridines, seeking optimum anti-platelet aggregation properties with minimal undesirable effects. They eventually selected for development the compound having the following structural formula:



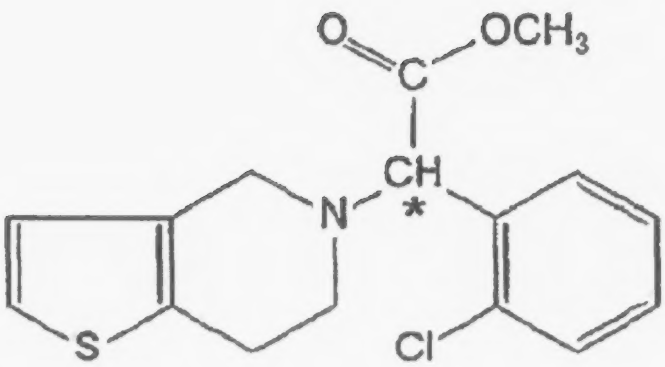
Sanofi gave this compound the common name "ticlopidine." After lengthy development, including animal and human trials, in 1991 ticlopidine was approved in the United States for use as an anti-thrombotic agent. This approval, however, was accompanied by required warnings concerning possible adverse effects, for reports had been received of rarely occurring but serious blood disorders, neutropenia and thrombotic thrombocytopenic purpura, associated with prolonged usage of ticlopidine. Thus Sanofi continued its search for a product that would have the therapeutic benefits of ticlopidine but without the adverse properties.

Sanofi synthesized and evaluated several hundred additional thienopyridine derivatives, including a class of compounds having the following general structure, wherein one of the hydrogen atoms on the bridge carbon atom (marked with an asterisk), is

replaced with an ester, carboxylic acid, or amide group. This class is the subject of the '596 patent (and the counterpart Canadian '875 patent), and is shown as follows:



X and Y can be any of a number of substituents, as identified in the patents; the district court found that there are thirty-seven possibilities for X and 1710 choices for Y. The patents state that compounds of this class exhibit good anti-platelet aggregation properties and are well tolerated. Focusing on the '596 patent, the specification includes twenty-one examples of specific compounds, including a compound designated as PCR 4099, which Sanofi synthesized in July 1980. In PCR 4099 the substituent attached to the bridge carbon is the methyl ester group (-$COOCH_3$), and X is chlorine in the 2-position, as follows:



This compound has the chemical name methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate, with the acronym MATTPCA. PCR 4099 as the hydrochloride salt was selected for commercial development as a potential replacement for ticlopidine in light of its improved platelet inhibition and toxicity profile.

However, PCR 4099 still raised toxicity concerns, for at very high doses it caused convulsions in laboratory animals. Thus the research efforts continued, concurrently with the clinical and commercial development of PCR 4099. Sanofi states that about 1500 compounds in this general class were synthesized, of which about 600, including PCR 4099, were chiral thienopyridines. "Chiral" is defined as "describ[ing] asymmetric molecules that are mirror images of each other, i.e., they are related like right and left hands. Such molecules are also called enantiomers and are characterized by optical activity." Richard J. Lewis, Sr., *Hawley's Condensed Chemical Dictionary* 270 (15th ed. 2007).

Enantiomers are spatial isomers, also called stereoisomers, wherein the isomeric compounds have the same chemical formula and the same chemical structure, but differ in their orientation in three-dimensional space. Such stereoisomers can exist for all molecules that contain an asymmetric carbon atom. An "asymmetric carbon" is a carbon atom to which four different substituents are attached, whereby, due to the tetrahedral structure of carbon bonds in three dimensions, the spatial orientation of substituents attached to a carbon atom varies. When there is only one asymmetric carbon atom in the molecule and thus only two stereoisomers, these isomers are called enantiomers.

Enantiomers are identified and distinguished by their optical characteristics when a purified solution of the separated isomers is exposed to plane-polarized light. One enantiomer will rotate plane-polarized light to the right (and thus is called the dextrorotatory or *d*- or (+) isomer), and the other rotates plane-polarized light to the left (called the levorotatory or *l*- or (-) isomer). For the compounds here at issue, the asymmetric carbon is at the bridge between the thienopyridine and the benzene components of the molecule, as marked with an asterisk in the drawings shown *ante*. Enantiomers generally are formed in equal amounts, to produce what is called a racemate; the racemate is optically neutral.

In the district court, experts for both sides explained the difficulty of separating enantiomers, for they are identical except for the spatial arrangement at one of the carbon atoms. Sanofi

scientists had previously separated the enantiomers of two thienopyridines, and had found that the separated enantiomers showed no advantage over the racemates. The first such separation was conducted in 1978 for a compound designated PCR 1033, which had a methyl group in place of one of the hydrogen atoms on the bridge carbon of ticlopidine, and whose maleate salt was found to be more potent than ticlopidine in antiplatelet activity but had undesirable side effects. On separation, it was found that one of the enantiomers of PCR 1033 was more biologically active but also more neurotoxic than the racemate. Thus, separation offered no benefit for PCR 1033.

About three years later, Sanofi separated the enantiomers of a compound designated PCR 3233, which had an ethyl group on the bridge carbon, and was more effective in antiplatelet activity than ticlopidine. However, neither of the separated enantiomers differed in activity from the racemate, and thus separation offered no benefit for PCR 3233. Sanofi witnesses testified to their belief that there was no advantage to separation of the enantiomers of thienopyridines, and no other racemates were separated until, in November 1985, Dr. Maffrand decided to study the enantiomers of PCR 4099.

The separation for PCR 4099 was assigned to Mr. Alain Badorc, the chemist who had separated the enantiomers of PCR 1033 and 3233. It was explained in the district court that such separations are complex and time-consuming, for enantiomers are identical except for the spatial orientation about one carbon atom, and tend to have identical or almost

identical chemical and physical properties. The district court received testimony that although the chemical literature shows at least ten separation techniques that might be tried, it cannot be known in advance which, if any, technique might work.

The record shows five months of experimentation by Mr. Badorc, and eventually the successful separation using a technique called diastereomeric salt formation. This procedure, which originated with Louis Pasteur, is based on the trial of diverse salt-forming compositions and conditions, in the hope of coming upon a lucky combination of reagents that will preferentially select one of the enantiomers and crystallize from the solution in optically pure form. In Mr. Badorc's successful experiment, he prepared thirty compositions of PCR 4099 and various resolving acids at various concentrations and in various solvents, and after about one month crystals formed in the composition containing (+)camphor-sulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone. This combination eventually yielded the pure levorotatory enantiomer, and isolation of the pure dextrorotatory enantiomer followed, as discussed by the district court in *Sanofi III*, 492 F. Supp. 2d at 372-73.

Sanofi then determined the biological properties of the enantiomers of PCR 4099, and found that they had the rare characteristic of "absolute stereo-selectivity": the dextrorotatory enantiomer provided all of the favorable antiplatelet activity but with no significant neurotoxicity, while the levorotatory enantiomer produced no antiplatelet activity but virtually all of the neurotoxicity. The experts for both

sides agreed that while it was generally known that enantiomers can exhibit different biological activity, this degree and kind of stereoselectivity is rare, and could not have been predicted. The experts explained that in the usual case, if one enantiomer is more biologically active than the other, that activity includes the adverse as well as the beneficial properties.

In view of these results, in April 1987 Sanofi terminated commercial development of the racemate PCR 4099, which had been proceeding since 1980 and had reached Phase I human trials at a cost stated to be tens of millions of dollars. More years of development ensued for the dextrorotatory enantiomer, to which Sanofi gave the common name "clopidogrel." Sanofi also found that the hydrochloride salt, which had been suitable for processing and tabletting the racemate PRC 4099, was not suitable for clopidogrel. After further research, Sanofi found that the hydrogen sulfate salt (also called the bisulfate) was suitable for tabletting. FDA approval of clopidogrel bisulfate was achieved in the United States in 1998, allowing introduction of the product Plavix®.

Sanofi filed a patent application directed to clopidogrel and certain salts and pharmaceutical compositions, in France on February 17, 1987 and then in the United States and other countries. The United States patent is the '265 patent in suit. The '265 specification explains that the racemate of the same chemical formula was described in the earlier French '247 patent, which corresponds to the earlier U.S. '596 patent. The '265 patent discusses the unusual stereoselectivity of the biological properties as be-

tween the dextrorotatory and the levorotatory enantiomers. The United States patent examiner, who had also examined the '596 patent, allowed the claims after requiring that the '265 claims make clear that the dextro- and levo-enantiomers are "substantially separated."

Apotex stipulated that claim 3 of the '265 patent is literally infringed by its product. The district court, after full trial including extensive expert testimony provided by both sides, ruled that claim 3 is valid and enforceable. Apotex appeals the court's rulings on the issues of anticipation and obviousness; the rulings in Sanofi's favor on the issues of unenforceability and double patenting are not appealed.

ANTICIPATION

Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003); *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1267-69 (Fed. Cir. 1991). An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-07 (Fed. Cir. 2006); *Elan Pharms., Inc. v.*

Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Anticipation is a question of fact, and the district court's finding of this issue is reviewed for clear error. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1369 (Fed. Cir. 2003).

A

The district court identified the limitations stated in claim 3 of the '265 patent as (1) the bisulfate salt of (2) the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. The references on which Apotex relied were the '596 patent or its Canadian '875 counterpart. Apotex argued that either reference not only shows the racemate PCR 4099, but also its addition salts and enantiomeric forms. The district court discussed that these references show PCR 4099 only as the racemate, and do not show the separated enantiomer or the bisulfate salt thereof. The district court found that although the racemate is in the prior art, the dextrorotatory enantiomer and salt in claim 3 of the '265 patent are not described, either explicitly or inherently, in any reference.

The court heard expert witnesses for both sides, who agreed that persons of ordinary skill in this field would have known that compounds that contain an asymmetric carbon atom have enantiomers. The '596 specification states: "These compounds having an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture." '596 patent, col. 1, lines 39-41. However, as the witnesses agreed, all of

the compounds in the '596 patent are racemates, and neither the twenty-one specific examples nor any other part of the specification shows their separation into enantiomers. The district court reasoned that a person of ordinary skill in the field of the invention would not have been guided to either the dextrorotatory enantiomer of PCR 4099 or its bisulfate salt.

Apotex argues that the district court erred in law, and that it suffices that the reference shows the specific racemate PCR 4099 and states that the compounds in the reference have enantiomers and that the enantiomers are included in the invention. Apotex states that the separation of enantiomers is routine, even if time-consuming or requiring some experimentation, and thus that that the separation need not have been performed or described in the reference. Apotex states that the properties of the enantiomers of PCR 4099 are inherently and necessarily present in its known racemate, such that when the enantiomers are separated the previously observed properties are "immediately recognized" in one or the other enantiomer.

Apotex stresses that the '596 patent's Example 1 is specific to PCR 4099, and the '596 claims refer to "addition salts with pharmaceutically acceptable mineral or organic acids" and "both enantiomeric forms or their mixture." The counterpart Canadian '875 patent states that when the desired structure is obtained it "is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action." Apotex concedes that the references do not show any separated

enantiomers or describe how to separate them, but argues that such detail is not required because persons of ordinary skill would know the existing techniques for separating enantiomers. Apotex thus argues that the dextrorotatory enantiomer of MATTPCA cannot be deemed novel, as a matter of law. However, as the district court recognized, that is not the correct view of the law of anticipation, which requires the specific description as well as enablement of the subject matter at issue. To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); *see also, e.g., In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference" (emphasis in original)).

The district court analyzed the question as whether a generic disclosure necessarily anticipates everything within the genus, and recognized that the answer depends on the factual aspects of the specific disclosure and the particular products at issue. *See, e.g., Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). In *In re Ruschig*, 343 F.2d 965, 974

(CCPA 1965), the court declined to find the disclosed genus anticipatory of everything within its scope, when the description of the genus would not lead a person of ordinary skill to a "small recognizable class with common properties." In this case the district court correctly declined to find that the references' general statements that these compounds consist of enantiomers constituted an anticipating disclosure of the separated dextrorotatory enantiomer of PCR 4099.

The district court discussed the cases on which Apotex particularly relied: *In re Petering*, 301 F.2d 676 (CCPA 1962), and *In re Schaumann*, 572 F.2d 312 (CCPA 1978). The court pointed out that in *Petering* and *Schaumann* the generic disclosure in the reference identified "specific preferences," which were met by the later-described species. We discern no clear error in the district court's finding that the references herein contained no such specific preferences. PCR 4099 is shown in the references as one of several compounds with desirable biological properties, but the district court did not clearly err in finding that the reference disclosure would not have led one of ordinary skill to recognize either an explicit or an inherent disclosure of its dextrorotatory enantiomer, as well as the bisulfate salt.

Apotex also relies on *In re Adamson*, 275 F.2d 952 (CCPA 1960), where the court held that although the reference did not state that the disclosed compound was a racemate, it would have been known to one of ordinary skill that synthetically produced chiral compounds are racemic. Sanofi does not dispute this statement of stereochemistry, but points out that

knowledge of the existence of enantiomers is not a description of a specific enantiomer "substantially separated" from the other, as in claim 3 of the '265 patent. The district court cited *In re May*, 574 F.2d 1082 (CCPA 1978), which is explicit that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate." *Id.* at 1090. Also, *Adamson* and *May* were addressing rejections for obviousness, and neither case stated or suggested a previously unseparated and unknown enantiomer might be deemed anticipated by the known racemate.

The district court did not clearly err in finding that the statements in the '596 patent and its Canadian counterpart that the products therein consist of enantiomers are not a description of the specific dextrorotatory enantiomer clopidogrel or a suggestion of its unusual stereospecific properties. The knowledge that enantiomers may be separated is not "anticipation" of a specific enantiomer that has not been separated, identified, and characterized. The district court correctly held that neither the '596 patent nor its Canadian counterpart contains an anticipating disclosure of the subject matter of claim 3 of the '265 patent.

B

The parties also debated the question of enablement with respect to anticipation. The district court found that the asserted references are not enabling, for they contain no guidance as to how to separate the enantiomers of PCR 4099. Based on the evidence adduced at trial, the court concluded that absent

such guidance, undue experimentation would be required.

Apotex argues that it is entitled to a presumption of enablement because the asserted references are patents, which are presumed to be enabling because they are presumed valid, citing *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 2003) ("We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff."). Apotex argues that the presumption should be particularly strong here, because the prior art patents belong to Sanofi. Thus Apotex argues that the general statements in the reference patents concerning enantiomers are presumptively enabling of the separate enantiomers of PCR 4099. Apotex states that it is irrelevant whether the separation of this specific enantiomer is shown in the references, because a person of ordinary skill in this field would know all of the existing techniques for separating stereoisomers, and would presumptively succeed in this particular separation. Apotex points out that the method that was eventually used by Sanofi was a well-known method, even if it involved some experimentation.

Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement. *See, e.g., Elan Pharms.*, 346 F.3d at 1054 (the reference must teach how to carry out the invention without undue experimentation). The factors relevant to whether experimentation is undue are

discussed in, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), and include the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology. The '596 patent reference states only that "if desired, its enantiomers are separated," and similarly for the Canadian counterpart. The district court found that these references contain no description of how to separate the enantiomers of PCR 4099, and that "[d]iscovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art." *Sanofi III*, 492 F. Supp. 2d at 387. This finding has not been shown to be clearly erroneous. In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007), this court recognized the known difficulty of separating enantiomers and the unpredictability of their properties, and held that a reference that stated that a compound has enantiomers did not enable the separation of those enantiomers, where the reference did not teach how to obtain the enantiomer. *Id.* at 1268-69. We discern no clear error in the district court's finding herein that the reference patents would not have enabled a person of ordinary skill to obtain clopidogrel substantially separated from the levorotatory enantiomer.

The district court's ruling that claim 3 of the '265 patent is not invalid for anticipation is affirmed.

OBVIOUSNESS

The determination of obviousness is a matter of law based on findings of underlying fact, wherein the factors identified in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), guide the inquiry:

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Id. at 17-18.

The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007); *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448 (Fed. Cir. 1984). For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. *See In re Sullivan*, 498 F.3d 1345, 1353 (Fed. Cir. 2007); *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963). Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness, shifting

to the patentee the burden of coming forward with evidence of nonobviousness. The evidence may take various forms, as relevant in the particular case. *See, e.g., Takeda Chem. Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1358, 1362-63 (Fed. Cir. 2007) (prima facie case depends on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, or to make the specific modification of the compound at issue); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (same). The ultimate determination is made in the context of the *Graham* factors, with the challenger having the ultimate burden of proving invalidity by clear and convincing evidence. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007).

The district court assumed that Apotex had made a prima facie case of obviousness based on the reference patents' disclosure of the PCR 4099 racemate, the statements in the patents concerning enantiomers, and the general knowledge that enantiomers may be separated and may differ from each other in biological properties. Upon consideration of the *Graham* factors, the court held that the unpredictable and unusual properties of the dextrorotatory enantiomer and the therapeutic advantages thereby provided, weighed in favor of nonobviousness, and that Apotex had not met its burden of establishing otherwise.

Apotex argues that the recognition in the prior art that PCR 4099 is composed of enantiomers outweighs the effect of any unexpected or unpredictable properties of the separated dextrorotatory enan-

tiomer. Apotex asserts that Sanofi's previous selection of PCR 4099 as a promising replacement for ticlopidine would have led a skilled artisan to start with PCR 4099 as a lead compound for further research. Apotex states that it was well known that enantiomers can have different levels of biological activity even if the exact allocation of properties is unpredictable, thereby rendering it obvious to separate the enantiomers and determine their properties. Apotex contends that the only features of clopidogrel bisulfate arguably not explicit in the prior art – the separation of the dextro- from the levorotatory enantiomer and its preparation as a bisulfate salt – required no more than well-known chemical techniques. Apotex cites known examples of other chiral compounds that exhibit stereoselectivity, and argues that the general knowledge that a favorable allocation of properties is possible suffices to render the separation obvious to a person of ordinary skill.

Apotex thus argues that there was motivation to separate the enantiomers of PCR 4099, and that a person of ordinary skill in the field would have been able to do so using known procedures, even if some experimentation was required, and then, upon separation of the enantiomers, routine testing would have revealed the favorable allocation of properties in the dextrorotatory isomer. Apotex asserts that it is not material that this allocation was unknown in advance and unpredictable, and that what matters is whether a person of ordinary skill would have had a reasonable probability of success in the separation and evaluation of the enantiomer, citing *Pfizer*, 480 F.3d at 1364, wherein this court observed that "case law is clear that obviousness cannot be avoided sim-

ply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."

Sanofi responds by challenging Apotex's view of the law, and citing the evidence on the factual premises of these arguments. At trial the expert witnesses for both sides agreed that a person of ordinary skill in this field in the mid-1980s would have known that enantiomers can exhibit different biological activities. However, the experts also agreed that it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested. The experts agreed that no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity. The experts agreed that weak stereoselectivity of biological properties is more common than strong stereoselectivity, and that absolute stereoselectivity is rare. Sanofi witnesses testified as to the research team's belief, based on the earlier separations of two other thienopyridines, that separation of enantiomers was unlikely to be productive. Apotex's expert, when asked whether one could predict in advance the therapeutic and toxic properties of the enantiomers, stated: "No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anybody presuming anything else." The experts also agreed that activity and toxicity were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity. Witnesses also explained that it was known that for compounds whose biological activity is delivered

through metabolism within the body, the acid environment in the stomach or other metabolic processes often restores the racemic state, thereby removing any potential benefit of a separated enantiomer. On the basis of this trial evidence, the district court found that a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity. Clear error has not been shown in this finding, and in the conclusion of nonobviousness based thereon. *See Papesch*, 315 F.2d at 391 (a chemical compound and its properties are inseparable).

The district court also discussed the evidence concerning the process of separating the enantiomers of PCR 4099. Apotex argued that Sanofi's separation procedure was well known, and therefore that the separated components of the known racemate were obvious as a matter of law, whether or not they were deemed to have unexpected properties. The district court observed that in 1987 there were at least ten techniques that had been used to separate enantiomers, and that they all required experimentation to determine whether they could be successful for a particular compound, including choices of reagents, solvents, concentrations, temperature, and a variety of other conditions. The court observed that Pasteur's diastereomeric salt formation technique had long been described in chemistry textbooks, but that the textbooks also explain that the method is difficult and that there is no "infallible recipe" for obtaining separation.

The district court referred to the testimony of Sanofi's expert, Dr. Stephen G. Davies, who stated, in discussing the diastereomeric salt formation method, that it is difficult indeed to cause one enantiomer to crystallize out of solution while the other does not. As discussed *ante* in connection with anticipation, Mr. Badorc's eventual success came only after several failures using other known strategies for enantiomer separation. The court observed that although Sanofi had previously separated the enantiomers of two other thienopyridines, the diastereomeric salt formation method had succeeded in one case but failed in the other. The court also found that a person of ordinary skill would have recognized that it could be more difficult to separate the enantiomers of PCR 4099 than the two other compounds that Mr. Badorc had previously separated, because it would be understood by chemists that the methyl ester substituent in PCR 4099 could make it more susceptible to re-racemization, and thus resistant to successfully obtaining a separated product.

The district court found that this separation was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable. The court observed that Apotex did not cite any reference showing or suggesting any reliable method of separation for any analogous compounds. The court described the separation as a "paradigm of trial and error," *Sanofi III*, 492 F. Supp. 2d at 370, and found that "neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether

to investigate them and, if obtained, they could not have predicted by what method and configuration." *Id.* at 371. The court found that Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR 4099, before separating the enantiomers, also weighed against finding that separation would have been obvious. Again, Apotex has demonstrated no clear error in the extensive finding of the district court concerning the difficulty and unpredictability of the separation of these enantiomers. These unchallenged findings undermine Apotex's argument in this appeal that the separation of the enantiomers would have been obvious. Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation. The application of hindsight is inappropriate where the prior art does not suggest that this enantiomer could reasonably be expected to manifest the properties and advantages that were found for this particular dextrorotatory isomer. *See Graham*, 383 U.S. at 36 (cautioning against hindsight whereby the teachings of the invention are read into the prior art); *see also KSR v. Teleflex*, 127 S. Ct. at 1742 (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness).

Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt. The PCR 4099 racemate is shown in the '596 patent as the hydrochloride, not the bisulfate. The district court

observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds, fifty-three of which acids had been used in FDA-approved drugs. The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable. The district court distinguished the facts of this case from those of *Pfizer*, 480 F.3d 1348, where there was evidence that based on the prior art a person of ordinary skill would have narrowed the possible salts to only a few including the claimed besylate, whereas here Sanofi presented evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage re-racemization. Apotex has shown no clear error in the district court's finding, based on the trial evidence, that the facts distinguish this case from those in *Pfizer*.

Based on all of these findings, the district court concluded: "Whether or not it may have been 'obvious to try' separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious." *Sanofi III*, 492 F. Supp. 2d at 392. Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that

enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 295 F.2d at 955, where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was "particularly expected" that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant "established a substantial record of unpredictability vis-à-vis a highly significant combination of properties."

The determination of obviousness is dependent on the facts of each case. *See Graham*, 383 U.S. at 17-18. In *Forest Laboratories*, 501 F.3d at 1269, this court affirmed that the (+) enantiomer of citalopram would not have been obvious in light of the known racemate, when it was shown that the therapeutic properties of the (+) enantiomer were unexpected. In contrast, in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007), this court held that the ramipril isomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers." Apotex argues that *Aventis* is the closer analogy, but the evidence was directly contrary to that position. The district court entered extensive findings in this case on the unexpected and unpredictable properties of clopidogrel, and there was no contrary evidence suggesting, based on the prior art, that the stereoselective properties were "precisely what one would expect," as in *Aventis*.

Apotex also argued in the district court, and repeats on this appeal, that Sanofi separated the enantiomers only because of a possible future regulatory requirement concerning the separation of enantiomers. Apotex states that this future regulatory requirement would have alerted a person of ordinary skill to the need to separate isomers, and thus would have rendered it obvious to do so. The district court found that the sole evidence referring to this regulatory possibility, an internal Sanofi memorandum, was written several months after Sanofi had discontinued its development of the racemic PCR 4099 in favor of the dextrorotatory enantiomer; the court also cited the testimony and documentary evidence that Sanofi undertook this separation in order to study the adverse neurological effects of PCR 4099, and not because of a possible future regulatory requirement. Sanofi also points out, as the general knowledge in this field confirms, that the recognition that stereoisomers may exhibit different properties does not teach which results may ensue or how to separate any given enantiomers. We discern no error in the short shrift that the district court gave to this argument.

Apotex also argues that the district court did not take adequate account of the Supreme Court's holding in *KSR v. Teleflex* that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 127 S. Ct. at 1739. Apotex states that Sanofi did no more than separate the enantiomers and determine their properties, and that the properties were predictably those of the racemate, allocated between the enantiomers. Sanofi

points out that this case does not concern a "combination of familiar elements" as in the *KSR* mechanical device made by combining known components to produce a combination having the properties of the known components. The evidence at trial well supported the finding that the result of this separation of enantiomers was unpredictable. We discern no error in the district court's implicit recognition that the principles of *KSR* do not affect the conclusion herein.

The district court thoroughly discussed the many issues and arguments raised by Apotex. We discern no error in the district court's findings that, on the state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity. The totality of these findings, and the correct application of law, ell support the district court's conclusion that invalidity had not been established by clear and convincing evidence.

AFFIRMED

APPENDIX B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT NEW YORK

SANOFI-SYNTHELABO; SANOFI-SYNTHELABO, INC.; and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs,

- against -

APOTEX, INC. and APOTEX CORP.,

Defendants.

No. 02 Civ. 2255 (SHS).

OPINION & ORDER

[June 19, 2007]

SIDNEY H. STEIN, U.S. District Judge.

After trial on the merits, this Court finds that Apotex, Inc. and Apotex Corporation (collectively, "Apotex") have failed to prove by clear and convincing evidence that U.S. Patent No. 4,847,265 is invalid or unenforceable on any of the grounds asserted. Accordingly, Sanofi-Aventis, Sanofi-Synthelabo, Inc. and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (collectively, "Sanofi") are entitled to permanent injunctive relief and, as shall be determined by the Court in a future proceeding, damages.

This action concerns a patent dispute between Sanofi – which invested in the research and development to patent and bring to market the drug known

as Plavix® – and Apotex, which seeks to market the generic equivalent of that drug. On the basis of the record established by the parties and the applicable law, the Court enters the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

FINDINGS OF FACT[1]

1. *History of this Action*

Plavix®, approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in November 1997, is prescribed for the reduction of thrombotic events such as heart attacks and strokes for patients who have recently suffered those events or who have arterial disease or acute coronary syndrome. (*See* Stipulated Statement of Facts ("Fact Stmt."), attached as Exhibit A to Joint Pretrial Order dated May 27, 2005 at ¶ 12.) The active ingredient of Plavix® is clopidogrel bisulfate. (*Id.*) Sanofi obtained a patent claiming bisulfate on July 11, 1989, naming Sanofi employees Alain Badorc and Daniel Fréhel as inventors. (*Id.* at ¶¶ 8-9.) That patent, U.S. Patent No. 4,847,265 ("the '265 patent"), claims clopidogrel bisulfate by its chemical name in Claim 3: "Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer." ('265 patent at col. 12, ll. 37-

---

[1] To the extent that any findings of fact may be deemed conclusions of law, they shall also be considered conclusions of law; to the extent that any conclusions of law may be deemed findings of fact, they shall also be considered as such. *See Miller v. Fenton*, 474 U.S. 104, 113-14, 106 S. Ct. 445, 88 L. Ed. 2d 405 (1985).

41.) Sanofi-Aventis is the owner of the patent-in-suit, which expires on November 17, 2011. The foreign priority filing date of the '265 patent – the date on which Sanofi filed its earlier application for the corresponding French patent – is February 17, 1987. The '265 patent is exclusively licensed to Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership. (Fact Stmt. at ¶¶ 3, 13.)

Apotex sought approval from the FDA to manufacture and sell clopidogrel bisulfate tablets before the expiration of the '265 patent by filing an Abbreviated New Drug Application ("ANDA") with the FDA in November 2001. (*Id.* at ¶¶ 14-15.) In the ANDA, Apotex certified pursuant to the requirements of 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that it believed the '265 patent to be invalid. (*Id.* at ¶ 16; *see also Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1344 (Fed. Cir. 2004).) Apotex was the first to file an ANDA for clopidogrel bisulfate (Decl. of Dr. Bernard Sherman, dated Aug. 16, 2006 ("Sherman Decl.") at ¶ 17), thereby securing the right to 180 days of market exclusivity provided by the Hatch-Waxman Act to the first ANDA filer to challenge a patent. *See* 21 U.S.C. § 355(j)(5)(B)(iv); *see also In re Tamoxifen Citrate Antitrust Litig.*, 429 F.3d 370, 376 (2d Cir. 2005).

In response to that ANDA filing by Apotex, Sanofi filed this litigation against Apotex on March 21, 2002 pursuant to 35 U.S.C. § 271(e), and asserted that Apotex's filing of the ANDA constituted infringement of the '265 patent, specifically Claim 3. (*See* Fact Stmt. at ¶ 17.) Apotex counterclaimed, asserting that the '265 patent is both invalid for three separate reasons and unenforceable as well.

First, Apotex alleges that the '265 patent is anticipated pursuant to 35 U.S.C. § 102(b) by an earlier patent held by Sanofi that covered a genus of chemical compounds called thienopyridines, within which clopidogrel bisulfate falls. (*See* Fourth Amended Answer and Amended Counterclaim ("Answer"), filed Nov. 17, 2006, at 3, 13.) The earlier patent, U.S. Patent No. 4,529,596 ("the '596 patent"), issued in July 1985 and expired in July 2003. (Fact Stmt. at ¶ 28.)

Second, Apotex contends pursuant to 35 U.S.C. § 103 that the subject matter claimed in the '265 patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. (*See* Answer at 3, 13.)

Third, Apotex contends that the patent is invalid under the judicial doctrine of obviousness-type double patenting. (*Id.* at 6, 15.)

Finally, Apotex also asserts that the '265 patent is unenforceable on the basis of Sanofi's alleged inequitable conduct before the U.S. Patent and Trademark Office ("PTO"). The alleged conduct consists of failing to name Dr. Jean-Pierre Maffrand as an inventor, making false statements to the PTO regarding the unexpected pharmacological properties of clopidogrel bisulfate, failing to disclose relevant prior research that Sanofi had conducted on a similar chemical compound, and failing to disclose a journal article that Apotex alleges is a material prior art reference. (*Id.* at 4-6, 8-15.)

With regard to infringement, the parties have stipulated that Apotex's clopidogrel bisulfate product infringes Claim 3 of the '265 patent. (*See* May 7,

2004 Stipulation and Order; Fact Stmt. at ¶ 18.) The ensuing procedural history of this action – including an account of the extensive settlement negotiations between the parties and the consequences for this litigation – is described in detail in this Court's Opinion dated August 31, 2006; familiarity with that Opinion is assumed. *See Sanofi-Synthelabo v. Apotex Inc.*, No. 02 Civ. 2255, 2006 U.S. Dist. LEXIS 65127, at *9-16 (S.D.N.Y. Aug. 31, 2006). In brief, Apotex initiated an at-risk launch of its generic clopidogrel bisulfate product on August 8, 2006. Shortly thereafter, Sanofi moved for a preliminary injunction prohibiting Apotex from distributing its generic product. After an evidentiary hearing was held, the Court granted Sanofi's motion for preliminary injunctive relief on August 31, 2006, but denied its request for a recall of the approximately six-month supply of product that Apotex had already shipped to distributors in the United States. *Id.* at *89-91.

Apotex then moved to stay the preliminary injunction, but both this Court and the U.S. Court of Appeals for the Federal Circuit denied that motion. Apotex then appealed the order granting the preliminary injunction to the Federal Circuit, which affirmed the grant of the preliminary injunction in an opinion dated December 8, 2006. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006), *reh'g denied*, 2007 U.S. App. LEXIS 2807 (Fed. Cir. Jan. 19, 2007). The parties then tried the merits of this action before this Court without a jury from January 22 through February 15, 2007. That trial – as well as the evidentiary hearing held in August 2006 – adduced the following facts.

II. *Sanofi's Efforts to Develop Antiplatelet Aggregation Drugs*

A. *Ticlopidine*

In 1972, Dr. Jean-Pierre Maffrand, then a Sanofi chemist in charge of a small research team, was asked by his supervisor to synthesize compounds structurally similar to tinoridine, a drug with known anti-inflammatory properties, in an effort to discover a superior anti-inflammatory drug. (Maffrand Tr. 1570-74.)[2] Tinoridine is a member of a class of compounds known as thienopyridines. (Maffrand Tr. 1575-76.) The chemical structure of a thienopyridine is characterized by the fusion of a thiophene ring to a pyridine ring. (Maffrand Tr. 1575-76.)

During 1972 and 1973, Sanofi synthesized a number of thienopyridine compounds. (Maffrand Tr. 1573-74.) Tests on those compounds revealed that unlike tinoridine, they possessed no anti-inflammatory properties. Some of the compounds, however – one of which Sanofi named "ticlopidine" – exhibited antiplatelet aggregation activity. (Maffrand Tr. 1573-75.) Put simply, the compound helped ensure that platelets in the blood would not aggregate together as much as they otherwise would. This was an important discovery. Researchers at Sanofi were convinced that platelets play a major role in events such as myocardial infarction and brain ischemia and Dr. Maffrand and his colleagues were interested to find an antiplatelet aggregation agent that would be "[a]

---

[2] References to (___ Tr. ___) refer to the page number of the trial transcript for the relevant witness. Similarly, references to (___ PI Tr. ___) refer to the page number of the transcript of the preliminary injunction hearing for the relevant witness.

better drug than aspirin." (Maffrand Tr. 1574-75.) In 1977, Sanofi obtained a patent on ticlopidine; that patent expired in 1994.

Ticlopidine was introduced as a drug in France in 1978 and in the United States in 1991, where it was marketed under the brand name "Ticlid." (Maffrand Tr. 1578-79; 1581-82.) Soon after the launch of ticlopidine in France, Sanofi became aware of rare but potentially fatal side effects associated with ticlopidine, specifically blood disorders known as neutropenia and thrombotic thrombocytopenic purpura ("TTP"). (Schneller Tr. 763, 815-16; Maffrand Tr. 1580-81.) As a result, the FDA required Ticlid to carry a "black box" warning that ticlopidine could cause life-threatening blood disorders. (Maffrand Tr. 1581.) The potential for these serious side effects meant that patients taking ticlopidine had to be clinically monitored for signs of blood disorders. (Maffrand Tr. 1581.) The sub-optimal side effect profile of ticlopidine – i.e., the risk of developing serious blood disorders – left open the need in the market for a drug that was as effective or more effective than ticlopidine, but with a lower risk of side effects.

B. *PCR 1033*

In 1975, Sanofi synthesized a thienopyridine named PCR 1033. That compound is the methyl analog of ticlopidine, which means that one of the two hydrogen atoms on the bridge carbon of a ticlopidine molecule – the carbon linking the thienopyridine and phenyl substituents – is substituted with a methyl (CH_3) group. (Maffrand Tr. 1584.) The addition of the methyl group makes the bridge carbon asymmetric. Here, some knowledge of

the basic principles of stereochemistry is required and has been best set forth by the Federal Circuit in its opinion affirming the preliminary injunction in this action:

> Stereochemistry refers to the three-dimensional spatial arrangement of a molecule's constituent atoms. Molecules that have the same chemical substituents, but different spatial arrangements, are referred to as stereoisomers. If they contain an asymmetrical carbon atom, they exist as non-superimposable mirror images of each other and are referred to as enantiomers. Enantiomers are optically active because they are capable of rotating plane-polarized light; enantiomers that rotate polarized light to the right are referred to as dextrorotatory enantiomers, or d-enantiomers; enantiomers rotating polarized light to the left are referred to as levorotatory enantiomers, or l-enantiomers. A mixture of equal amounts of both types of enantiomers is referred to as a racemic mixture, or racemate, and it exhibits no optical activity.

Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d at 1372.

Unlike ticlopidine, PCR 1033 is a racemate composed of the 50:50 mixture of its enantiomers. (Maffrand Tr. 1584, 1599-1600, 1682-83.) To make PCR 1033 suitable for testing, Sanofi chemist Alain Cabrol attempted to prepare the hydrochloride salt of PCR 1033, but that effort failed. (Maffrand Tr. 1599-1600; 1699; Badorc Tr. 1810.) Instead, Sanofi prepared PCR 1033 as a maleate salt. (Maffrand Tr.

1600.) When tested, Sanofi found that PCR 1033 was a more potent antiplatelet aggregation agent than ticlopidine, but that it was also less well-tolerated than ticlopidine; side effects were observed during the initial pharmacological testing of PCR 1033 in different species. (Maffrand Tr. 1587.) Around the beginning of 1976, Sanofi ceased efforts to develop PCR 1033 because of those side effects. (Maffrand Tr. 1587.)

In 1978, Maffrand asked Alain Badorc, a Sanofi chemist, to try to obtain the enantiomers of PCR 1033. (Maffrand Tr. 1587-88; Badorc Tr. 1807.) Maffrand testified at trial that "we wanted to try our luck" to see if either enantiomer had a better ratio of antiplatelet activity to tolerance than the racemate. (Maffrand Tr. 1588.) At that time, Maffrand knew that a two-fold increase in a single enatiomer's therapeutic activity was the quantitatively best possible increase that could be attained through separation of the enantiomers of a racemate, and that such a result "is not the most frequent case." (Maffrand Tr. 1591-93; Harden Tr. 2304-06.) For that reason, Sanofi's preferred mode of searching for superior antiplatelet drugs at that time had been to modify the substituents of racemic compounds (thereby creating new compounds) – not to isolate the individual enatiomers of particular racemates – because a modified compound was the more likely path to significantly greater gains in antiplatelet activity. (Harden Tr. 2304; Maffrand Tr. 1592-94.)

Badorc successfully separated the enantiomers of PCR 1033 on his first attempt by means of a technique known as diastereomeric salt formation. (Badorc Tr. 1809; Maffrand Tr. 1702.) That method

involves combining the enantiomers of a racemic base with an enantiomerically pure chiral acid to form a diastereomeric salt (i.e., a salt with two chiral centers) in two distinct stereoconfigurations. (Davies Tr. 1934.) The resulting diastereomers, if formed, do not have identical physical properties; their different solubilities in a particular solvent, for example, may facilitate their separation. (Davies Tr. 1934-35; McClelland Tr. 1105-06.) However, the Court credits the testimony of Dr. Stephen G. Davies, an expert for Sanofi, who stated, "[t]he problem is that it is very hard to find situations where one [diastereomer] crystallizes out and the other one does not . . . . you are trying to get one to do something while leaving the other one behind." (Davies Tr. 1935-36.) If the diastereomers are successfully separated, a base is added to one of the two separated diastereomeric salts to reconstitute the original base, which is then in an enantiomerically pure form. (McClelland Tr. 1108-1109; Davies Tr. 1936-37.)

Badorc prepared the diastereomeric salts of PCR 1033 by using tartaric acid dissolved in ethanol. (Badorc Tr. 1808-09.) The levorotatory enantiomer was designated PCR 3071 and the dextrorotatory enantiomer was designated PCR 3072. (Maffrand Tr. 1598.) To facilitate further testing, Badorc prepared the hydrochloride salts of PCR 3071 and PCR 3072. (Badorc Tr. 1810.) As noted, previous efforts to prepare the hydrochloride salt of the racemate – PCR 1033 – had failed. (Maffrand Tr. 1600, 1699.) Testing on the enantiomers revealed that PCR 3071 exhibited antiplatelet activity and PCR 3072 was inactive; the active enantiomer, however, was less well tolerated than ticlopidine and was not

appropriate for administration to humans. (Maffrand 1598-99.) Sanofi discontinued the development of those enantiomers in 1981. (Maffrand Tr. 1599.)

C. *PCR 3549*

In 1978 – after Sanofi had synthesized PCR 1033 but before it had discontinued the development of PCR 3071 and PCR 3072 – Sanofi synthesized the ethyl analog of ticlopidine, which was designated PCR 3233. (Maffrand Tr. 1601-02.) Attempts to make the hydrochloride salt of PCR 3233 – an oily base – failed, but, after several failed attempts, Badorc eventually obtained its nitrate salt, which was designated PCR 3549. (Maffrand Tr. 1604; Badorc Tr. 1812.) Testing revealed that PCR 3549 was more potent than ticlopidine and better tolerated than PCR 1033, but was still less well tolerated than ticlopidine. (Maffrand Tr. 1604-05.) In November 1978, Maffrand asked Badorc to prepare the enantiomers of PCR 3549 to see if either enantiomer had a better risk/benefit profile than the racemate. (Maffrand Tr. 1605-06; Badorc Tr. 1811.) Badorc tried to separate the enantiomers of PCR 3549 using diastereomeric salt formation – the technique that he had used successfully to resolve the enantiomers of PCR 1033 – but several attempts failed. (Maffrand Tr. 1606; Badorc Tr. 1813-14.) Badorc then tried to obtain the enantiomers of PCR 3549 by a different method – chemical asymmetric synthesis. (Maffrand Tr. 1606; Badorc Tr. 1819-20.) That method involves taking a precursor compound that is enantiomerically pure and modifying the compound to obtain the desired compound, but without altering the stereochemical configuration of the precursor compound. (Davies Tr. 1932-33; Badorc Tr. 1819-20.)

At that time, Badorc believed – and he testified at trial that he still believes – that he successfully synthesized the enantiomers of PCR 3549 by that method. (Badorc Tr. 1823-24.) Badorc further testified that he confirmed his successful synthesis of the enantiomers of PCR 3549 in 1978 by measuring the rotatory power of each enantiomer, which were equal in absolute value (Badorc Tr. 1824); that result – the equal and opposite optical rotation of two products – is evidence of the presence of two enantiomers. (Davies Tr. 1981; Hendrickson Tr. 1474.) In addition, the nitrate forms of each enantiomer had equivalent melting points that were each higher than the melting point of PCR 3549. (Davies Tr. 1981.) Furthermore, "the chance is minimal, if not nonexistent," that two parallel asymmetric syntheses – such as those Badorc performed – would result in products demonstrating the same level of rotatory power and the same melting points. (Davies Tr. 1819.) The Court credits the testimony from Dr. Davies that this data provided strong evidence that Badorc had indeed obtained the enantiomers of PCR 3549 by means of asymmetric synthesis. (Davies Tr. 1981-82.)

Sanofi designated the levorotatory enantiomer PCR 3620 and the dextrorotatory enantiomer PCR 3621 and tested them for platelet aggregation inhibition activity. (Badorc Tr. 1826.) That testing showed that the platelet aggregation inhibiting activities of PCR 3620 and PCR 3621 were each comparable to PCR 3549, meaning neither improved on the racemate. (Maffrand Tr. 1615-16.) For that reason, Sanofi discontinued development of PCR 3620 and PCR 3621 and focused its efforts on PCR 3549. (Maffrand

Tr. 1616-17.) PCR 3549, however, proved to be less well-tolerated than ticlopidine at similar dosage levels, and lower doses of PCR 3549 were insufficiently therapeutic. For those reasons, Sanofi abandoned its efforts to develop PCR 3549. (Maffrand Tr. 1616-17.)

D. *PCR 4099*

Sanofi synthesized several other thienopyridines in addition to PCR 1033 and PCR 3549. After having created two carboxylic acid derivatives of ticlopidine – in 1976 and 1978, respectively – which showed no platelet inhibition, Sanofi synthesized a new compound in 1980 that had an ethyl ester ($O=C-O-CH_2-CH_3$) substituent on the bridge carbon. (Maffrand Tr. 1637-39.) That compound – PCR 3935 – proved active in tests of antiplatelet aggregation activity (Maffrand Tr. 1638), and, after attempts to prepare it as both hydrochloride and bisulfate salts had failed, Sanofi prepared it as a hydrobromide salt. (Maffrand Tr. 1640.) Concerned, however, that PCR 3935 might be converted in the human body into carboxylic acid – which could render the compound therapeutically inactive – Sanofi synthesized a new compound in July 1980 by replacing the ethyl ester substituent of PCR 3935 with a methyl ester ($O=C-O-CH_3$) substituent. (Maffrand Tr. 1638-40.) Sanofi designated that compound – a racemic mixture prepared as a hydrochloride salt – as PCR 4099. (Maffrand Tr. 1640-41.) The non-salt (free base) form of PCR 4099 is described by the chemical formula methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o-chlorophenyl-acetate, or "MATTPCA." The nomenclature "methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o-chlorophenyl-acetate" is

equivalent to "methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate." (Fact Stmt. at ¶ 31.)

Testing showed that PCR 4099 exhibited more antiplatelet activity and was better tolerated than ticlopidine. (Maffrand Tr. 1641.) Nonetheless, Sanofi continued to synthesize and test other racemic carboxylic acid and ester derivatives of ticlopidine, as well as derivatives with amide ($O=C-NR_2$) substituents. (Maffrand Tr. 1641-43.) In total, Sanofi synthesized approximately 70 carboxylic acid, ester, and amide derivatives of ticlopidine, all of which were racemic mixtures. (Maffrand Tr. 1636-1637; 1642.) Many of these compounds were subjected to a battery of tests of pharmacological activity, including four tests known as the bleeding-time test, the silk-thread test, the collagen test, and the ADP test.[3] (Maffrand Tr. 1641; Hanson Tr. 2226, 2232-33, 2238-39, 2243, 2246-67.) These were screening tests "designed to quickly screen a large number of candidate compounds in order to identify a manageable number of compounds [for] more sophisticated testing." (Hanson Tr. 2226-27; *see also* Maffrand Tr. 1644, 1646.) Sanofi's expert Dr. Stephen R. Hanson gave testimony at trial – which the Court credits – that conclusions drawn from such tests are "tentative" and that "it would be risky to extrapolate the results of these tests" – performed only in rats – to other animals or humans. (Hanson Tr. 2227.)

---

[3] ADP refers to adenosine diphosphate.

III. *The '596 Patent and Its Non-U.S. Counterparts*

In July 1982 and July 1983, Sanofi applied for French and U.S. patents, respectively, on the class of thienopyridines having carboxylic acid, amide, and ester substituents. An internal Sanofi memorandum authored by Dr. Maffrand and dated February 11, 1982 stated that the patent would cover "PCR 4099 and its analogues." (Defendant's Exhibit ("Def. Ex.") 632.) The memorandum also noted that based on pharmacological testing, "[t]he most interesting esters were: PCR 4099, 4316, SR 24593, [and] SR 24597" and "[t]he most interesting amides were: PCR 4317, 4535, [and] 4516." (*Id.*) The application that was filed in the United States matured into the '596 patent, which issued on July 16, 1985 and listed Maffrand, Aubert, and Ferrand, among others, as inventors. The '596 patent is entitled "Thieno [3,2-c] Pyridine Derivatives and Their Therapeutic Application," and describes a genus of compounds that exhibit blood-platelet aggregation inhibition and anti-thrombotic activity. (Fact Stmt. at ¶ 27; '596 patent at col. 8, ll. 26-39.)

Sanofi also obtained European patent EP099802 ("the '802 patent") and Canadian Patent No. 1,194,875 ("the '875 patent") over the same class of compounds. These patents were also published more than a year before February 17, 1987, the foreign priority filing date of the '265 patent.

A. *The Specification of the '596 Patent*

The general formula described in column 1 of the '596 patent specification – which has two variables (X and Y) – depicts a racemate in non-salt (free base) form. The general formula covers an extremely large

number of compounds covered by providing for various substituents in place of the X and Y groups. (McClelland PI Tr. 494; Davies Tr. 1913-14). Each of the X and Y variables can be one of a number of enumerated substituents, with thirty-seven possibilities for the X variable and 1710 possible choices for Y. Multiplying these variables by the number of pharmaceutically acceptable acid addition salts yields an even higher number. Dr. Maffrand testified at trial that the patent covers "millions of compounds if we take into account all the combinations possible of products and salts." (Maffrand Tr. 1771.) Similarly, Sanofi's expert Dr. Davies testified that the patent covers "several millions of compounds." (Davies Tr. 1914.)

The general formula does not describe any individual enantiomer and does not describe how to obtain the enantiomers of any racemate; as drawn, the general formula describes a racemic mixture only. (Davies Tr. 1913.) However, the specification states that with respect to the general formula, "[t]he invention relates both to each enantiomer and their mixture." ('596 patent at col. 1, ll. 40-41.) The specification also sets forth that the thienopyridine compounds within the genus covered by Claim 1 can be made into addition salts with pharmaceutically acceptable mineral or organic acids or a mineral base. ('596 patent at col. 1, ll. 42-51.)

In addition, the '596 patent specification gives twenty-one examples of compounds included within the genus compound "to exemplify and to illustrate the different substituents which were claimed in the general formula." (Maffrand, PI Tr. 138; '596 patent at cols. 3-8.) These different compounds are de-

scribed in the patent as different salts forms – including hydrobromide, hydrochloride, and bisulfate salts. (Maffrand, PI Tr. at 139-140.) Specifically, three of the examples are shown as hydrochloride salts and four of the examples are shown as bisulfate salts. (Snyder Tr. 236.) The first of the twenty-one examples in the '596 patent – Example 1 – is PCR 4099, prepared as a hydrochloride salt. (Maffrand, PI Tr. at 139.) Neither Example 1, nor any other example set forth in the specification, refers to the individual or separated enantiomers of PCR 4099 or, for that matter, of any other exemplified compound. Furthermore, there is no example in the '596 patent of a methyl ester – such as PCR 4099 – prepared as a bisulfate salt. (Banker Tr. 1328.) In addition, the pharmaceutical formulations provided as non-limiting examples at the end of the specification do not show a bisulfate salt in the solid dosage form. (McClelland Tr. 1178-79; '596 patent at col. 12, ll. 3-28.)

The specification of the '596 patent also describes the compounds covered by the patent as exhibiting "an excellent tolerance and a low toxicity." ('596 patent at col. 8, ll. 42-43.) In the 1980s, Sanofi scientists commonly used the terms "tolerance" and "tolerated" to denote a compound's relative toxicity and described compounds that performed well in sub-acute and acute toxicity tests as "not very toxic" or "better."[4] Dr. Maffrand testified that he considers "toxic-

[4] The practice of referring to "tolerance" in the context of acute toxicity testing is not unique to Sanofi. Patents of companies other than Sanofi use the term "well-tolerated" to refer to results obtained through acute toxicity testing. *See, e.g.*, U.S. Patent No. 4,242,360 (Dec. 30, 1980) at col. 3, ll. 12-23 (basing

ity" to be "included in tolerance." (Maffrand Tr. 1664.) Dr. Frédéric Lacheretz, the deputy head of Sanofi's toxicology department in the mid-1980s, testified that the terms " 'more toxic than' [or] 'less well-tolerated than' . . . mean the same thing." (Lacheretz Tr. 2392.) In addition, Dr. Hanson testified that the terms toxicity and tolerance are "not necessarily mutually exclusive." (Hanson Tr. 2224.) Similarly, Apotex's expert, Dr. Gilbert Banker, agreed that "not toxic" means that a substance "won't make you sick, won't affect your physiologic functions, won't deleteriously affect your organs or even produce untoward side effects," and that non-toxic has the same meaning as "well tolerated." (Banker Tr. 1294.)

The Court credits Dr. Hanson's testimony that "[u]nless you're talking about a formally-described toxicology or tolerance study, the term tolerance . . . is commonly used as a general term that can describe toxic side effects as well as less severe side effects." (Hanson Tr. 2225-26.) Furthermore, the Court finds that the use of the terms "well-tolerated" and "less well-tolerated" is not restricted to descriptions of a drug's performance in tests at therapeutic doses only. (Graham Tr. 2424.) Apotex has failed to persuade the Court that those terms cannot appropriately be used to describe performance in tests at supra-therapeutic doses, including subacute and acute toxicity tests. (*See* Graham Tr. 2424; Hanson Tr. 2224; Lacheretz Tr. 2359; Rodricks Tr. 2495.)

---

an assessment of tolerance on the results of acute toxicity testing) (Pl. Ex. 447); *see also* Snyder Tr. 714-17.

B. *The Claims of the '596 Patent*

As described above, Claim 1 sets forth a general formula that covers millions of compounds, including "their addition salts with pharmaceutically acceptable mineral or organic acids . . . including both enantiomeric forms or their mixture." ('596 patent at col. 12, ll. 30-68, col. 13, ll. 1-19.) Claim 8 covers the same genus of compounds as Claim 1, but claims their "therapeutic compositions." Claim 8 reads:

> A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

('596 patent at col. 14, ll. 5-11.)

Claims 2 through 7 correspond to particular racemates, and Claim 2 specifically claims MATTPCA, or the free base of PCR 4099:

> Methyl α-(4,5,6,7-tetrahydro-thieno(3,2,c)-5-pyridyl)-o.chlorophenyl-acetate.

('596 patent at col. 13, ll. 19-20.)

Claims 2 through 7 do not include the language "both enantiomeric forms or their mixture' or "their addition salts." Claim 2, therefore, does not expressly claim any salt form of MATTPCA. (Davies Tr. 1917-19; Byrn Tr. 2134.) In addition, Claim 2 does not include a stereochemical descriptor (e.g., "*d*-" or "*l*-")

that identifies it as referring to an individual enantiomer.

C. *Tests of Pharmacological Activity Reported in the '596 Patent*

As noted above, prior to Sanofi's application for the '596 patent, several racemic compounds covered by the general formula of Claim 1 were tested for platelet aggregation inhibition activity. Results of those tests – the bleeding-time test, the silk-thread test, the collagen test, and the ADP test – were reported in the specification to the '596 patent. (Hanson Tr. 2226, 2232-33, 2243, 2246.)

Table I reports the results of the ADP test in which nine compounds, including PCR 4099 – which is listed as Derivative 1, were tested; most of the compounds demonstrated significant activity. At the doses at which they were tested, Derivative 4 demonstrated activity that was not meaningfully different from that of PCR 4099. (Snyder Tr. 633-35; '596 patent at col. 9, ll. 31-55.) In the collagen test reported in Table II, twelve compounds were tested, and, again, most of the tested compounds demonstrated significant activity. At the doses that were tested, Derivatives 9, 4, and 10 demonstrated activity quantitatively superior to that of PCR 4099, although Sanofi's expert Dr. Hanson described the activity levels of those compounds as comparable to that of PCR 4099. (Hanson Tr. 2244-46; '596 patent at col. 10, ll. 1-31.) In the bleeding-time test, reported in Table III, six compounds were tested. All the tested compounds, including PCR 4099, demonstrated maximal inhibition of blood clotting activity. (Snyder Tr. 641; Hanson Tr. 2232-33, 2237-38; '596

patent at col. 10, l. 55, col. 11, l. 5.) In the silk-thread test reported in Table IV, most of the six tested compounds demonstrated significant activity. At the doses that were tested, two of the six compounds, Derivative 3 and Derivative 10, demonstrated activity quantitatively superior to that of PCR 4099. (Snyder Tr. 641-42; '596 patent at col. 11, ll. 35-51.) Again, Sanofi's expert Dr. Hanson testified, however, that "[f]or compounds No. 3, 10, [PCR] 4099, and No. 2, all of which did very well, it is not possible to further rank their effects." (Hanson Tr. 2241.)

As noted above, Dr. Hanson testified that the pharmacological activity data presented in Tables I-IV of the '596 patent is not an appropriate scientific basis on which to rank the relative performance of the compounds – except in cases where a high dose produces little or no activity. (Hanson Tr. 2226-27, 2241, 2246.) These were screening tests used to make rough determinations of activity versus inactivity. In addition, because the screening tests were performed in rats, inferences as to how the tested compounds would perform if administered to humans would be tentative because many drugs behave differently in rats and human beings. As a result, it "would be risky to extrapolate the results of these tests" to any other animal or to human beings. (Hanson Tr. 2227-29.)

Furthermore, the tests did not provide enough data points to construct a dose-response curve for each compound; a dose-response curve is a tool used to compare the relative potency of different compounds. (Hanson Tr. 2235.) The lack of data points made it impossible to derive an "ED_{50}" value, the dose at which each compound produces half its

maximal response, which is a similar tool of comparison. (Snyder Tr. 630-32; Maffrand Tr. 1646; Hanson Tr. 2236-37.) Finally, nearly all of the compounds were tested at only one or two dose levels (Snyder Tr. 642-43), making it impossible to draw conclusions about how the compounds would perform at lower doses. (Hanson Tr. 2238.) For these reasons, the Court finds that a person of ordinary skill in the art would not discern a preference for PCR 4099 based on the pharmacological testing data in the '596 patent. (Hanson Tr. 2250.)

D. *The Canadian '875 Patent*

As noted above, the '875 patent is the Canadian counterpart to the '596 patent. (Def. Exs. 206; 1235.) Claim 1 describes a "procedure for preparing derivatives of general formula (I)"-the same general formula claimed in Claim 1 of the '596 patent. With regard to the general formula, the '875 patent also claims "the two enantiomers or their mixture." In addition, after describing the procedure for preparing certain compounds, the claim states that "then the corresponding derivative sought is obtained, which is isolated and, if desired, its enantiomers separated and/or it is salified by mineral or organic acid action." (Def. Ex. 1235.)

E. *The European '802 Patent*

U.S. Patent No. 5,989,578 ("the '578 patent") – a patent held by Sanofi which issued in 1999 – states that clopidogrel is "described" in EP 099 802, the European counterpart to the '596 patent. Two factors militate against giving that statement any credence. First, the application for the European '802 patent was filed in July 1983, well before Sanofi's separa-

tion of PCR 4099 into its enantiomers or the formulation of the dextrorotatory enantiomer of PCR 4099 – clopidogrel – as a bisulfate salt, as described below. (Maffrand Tr. 1672-73.) Second, a named inventor of the '578 patent – Dr. Pierre Savi – testified that the statement in that patent that clopidogrel is described by the European '802 patent is "incorrect," and that he had not personally read the European patent until his deposition relating to this action. (Savi 8/21/03 Dep. 164-65, 314-17.) Dr. Savi also testified that other named inventors listed on the '578 patent are biologists, not chemists. (*Id.* at 317.) Accordingly, the Court does not credit the alleged disclosure in the '578 patent and does credit Dr. Savi's unequivocal later statement that clopidogrel is not described by the '802 patent.

IV. *The Development of PCR 4099 and Its Enantiomers*

Sanofi's decision to further develop PCR 4099 required clinical testing, which in turn required Sanofi to synthesize large quantities of the drug in tablet form. From 1980 until 1987, PCR 4099 was the subject of more than fifty different types of tests in animals and humans, and Sanofi spent "tens of millions of dollars" on those tests. (Maffrand PI Tr. 144.) Sanofi also performed additional pharmacological and toxicological studies, as well as metabolic and pharmacokinetic studies. (Maffrand PI Tr. 143.) Between 1983 and 1987, Sanofi conducted acute and long-term chronic toxicity tests on PCR 4099 in rats, mice, and baboons. In each test and in each species, convulsions were observed at certain dose ranges. (Lecheretz Tr. 2362-70; Rodricks Tr. 2481-83.) A one-year chronic toxicity study in baboons in 1987

showed convulsions at all doses, including the lowest dose tested, 25 mg/kg, and demonstrated that more convulsions were observed at higher doses. (Rodricks Tr. 2481-82.)

During 1985, Sanofi representatives, including Dr. Maffrand, made poster presentations and distributed corresponding abstracts concerning their work on thienopyridines – and, in particular, PCR 4099 – at conferences of the International Society for Thrombosis and Hemostasis held in San Diego and Jerusalem. (Maffrand Tr. 1680; *see also* Def. Exs. 183, 184, 185, 186, 188, 224, 308, 418, 427.) The abstract prepared for the San Diego conference regarding PCR 4099 stated that the compound "exhibits the same broad spectrum of antiaggregating effect as ticlopidine in animals but is 40 times more potent in rats and 10 times in baboons." (Def. Ex. 184.) According to Sanofi's expert Dr. Hanson, the abstracts prepared for both conferences informed a person of ordinary skill in the art that "PCR 4099 exhibits activity in both humans and animals against platelet aggregation, and specifically the activity seems to be specially active toward the ADP pathway of platelet aggregation." (Hanson Tr. 2219-20.) Dr. Maffrand testified that Sanofi's "main goal was to inform the scientific community of the potent antiplatelet and antithrombotic activities of PCR 4099" and "to show that the compound was much more effective than ticlopidine." (Maffrand Tr. 1680.)

PCR 4099 was the only compound covered by the '596 patent that was publicized at the San Diego and Jerusalem conferences. (Maffrand Tr. 1736, 1748-49.) The posters and abstracts did not, however, discuss in any way the stereoselectivity of platelet inhibition

by the enantiomers of PCR 4099 or, for that matter, make any reference at all to the enantiomers of PCR 4099. (Maffrand Tr. 1681-86; Hanson Tr. 2220.) Accordingly, a person of ordinary skill in the art would not have drawn any inference from those materials concerning the stereoselectivity of platelet inhibition by the enantiomers of PCR 4099. (Maffrand Tr. 1681-86; Hanson Tr. 2220.) To the contrary, based on the posters and abstracts, a person of ordinary skill in the art would have concluded that PCR 4099 was under development as a promising racemic drug with several positive qualities and no significant reported negative qualities. (Snyder Tr. 290-91.)

Dr. Maffrand, however, also was aware as of 1985 that testing had showed that PCR 4099 had potential negative side effects in humans. (Maffrand Tr. 1651.) Various studies – including acute toxicity, dose-range finding, and chronic oral toxicity studies – conducted in 1983 and 1985 had demonstrated the tendency of PCR 4099 to cause convulsions in animals at particular dose levels. (*See* Plaintiff's Exhibits ("Pl. Exs.") 114, 115, 116, 117; Rodricks Tr. 2481-82.) For example, the report of a four week oral toxicity study of PCR 4099 conducted in baboons in 1983 included the observation that "[d]eath was preceded by convulsions and was most likely not accidental." (Pl. Ex. 113.) Furthermore, as a general matter, Sanofi was aware of the possibility that drugs that appeared safe in pre-clinical and clinical development might nonetheless show rare but serious side effects after launch – as had recently been the case with ticlopidine. (Maffrand PI Tr. 144; Maffrand Tr. 1651.) With the goal of finding a compound with a

better profile than PCR 4099, Dr. Maffrand decided in November 1985 to have the enantiomers of PCR 4099 separated and tested. (Maffrand Tr. 1651.)

A. *Predicting the Biological Properties of the Enantiomers of PCR 4099*

Whether it was possible for Sanofi to predict the biological properties of the enantiomers of PCR 4099 – and whether one could predict that the properties of a single enantiomer would be superior to those of its opposite enantiomer – is hotly contested by the parties to this litigation. However, in view of the prior art and the testimony given in this action, the following facts are clear.

A person of ordinary skill in the art in the mid-1980s would have known that the enantiomers of a racemate could exhibit different biological activity – including different levels of both therapeutic activity and toxicity. (Snyder Tr. 169.) As of 1984, for example, Ariëns taught that "[o]ften, only one isomer is therapeutically active, but this does not mean that the other is really inactive. It may very well contribute to the side-effects." E.J. Ariëns, "Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology," *Eur. J. Clin. Pharm.* 663 (1984) (Def. Ex. 138); *see also id.* at 664. Similarly, Williams & Lee taught that:

> Basic pharmacological data on the differences in activity between enantiomers suggest that there are many other drugs for which an increase in therapeutic index might be obtained by using the appropriate enantiomer rather than the racemic drug.

Kenneth Williams & Edmund Lee, "Importance of Drug Enantiomers in Clinical Pharmacology," *Drugs* 333, 348 (1985) (Def. Ex. 164); *see also* Goldstein, et al., *Principles of Drug Action (2d Ed.)* 754 (1974) (Def. Ex. 1305).

Dr. Maffrand testified at the preliminary injunction hearing that literature in the late 1970s taught that the therapeutic properties of stereoisomers could "show no obvious difference" or "could have different affinity and different activity for their known receptor." (Maffrand PI Tr. 170-71.) Where there is variation, the extent of that variation is not predictable and can be weak, moderate, or strong – a view confirmed by experts from both parties and credited by this Court. (Harden Tr. 2295-96.) Dr. Robert Snyder, an expert for Apotex, testified that without separating and testing the enantiomers of a particular racemate, a person of ordinary skill in the art could not know what the degree of difference – if any – between the properties of the enantiomers of a racemic compound would be. (Snyder Tr. 556.) The prior art, in fact, suggested that "weak" stereoselectivity – i.e., a difference in activity of ten-fold or less between two stereoisomers – was fairly common and that strong stereoselectivity – i.e., a difference in activity of 100-fold or more between stereoisomers – was less prevalent. (Harden Tr. 2295-99; Hanson Tr. 2215-16; Snyder Tr. 557-58.) In particular, the following prior art reference from Lehmann is relevant:

> When the biological activities of stereoisomers (enantiomeric and diastereomeric . . .) are compared, it is sometimes found that only one member of each pair is very active, rarely that

> both members are equally active. Very frequently though, both members exhibit the same type of activity but to a different degree. Several thousand such cases have been recorded . . . . The differences in activity for the members of any one pair . . . vary enormously, viz. from ca. 1 up to nearly 10^6.

P.A. Lehmann, et al., "Stereoselectivity and Affinity in Molecular Pharmacology," *Prog. Drug. Res.* 101, 104 (1976) (Def. Ex. 268).

The Court finds, furthermore, that a person of ordinary skill in the art would have known that absolute stereoselectivity – meaning the presence of a particular kind of activity exclusively in one stereoisomer and its total absence in the other – was uncommon. (Harden Tr. 2299-2300; Lehmann (1976) at 122.) It was also rare, moreover, if both enantiomers exhibited precisely the same levels of activity. (Snyder Tr. 172, 556-58; Lehmann (1976) at 104.) Experts from both parties agreed that even today, no scientific principles afford a basis for predicting to what degree, if any, a pair of stereoisomers will exhibit different levels of therapeutic activity and different levels of toxicity. (Snyder Tr. 563-65; Davies Tr. 2018-19; Hanson Tr. 2214.) As Dr. Davies testified, "Anything is possible . . . . You can't predict anything unless you do the experiments." (Davies Tr. 2019.) The prior art confirms this testimony as least as it relates to the separation of enantiomers as of the mid-1980s. *See* Lehmann (Def. Ex. 268) at 104 ("In spite of extended efforts . . . it has so far not been possible to explain these ratios; every biological system, sometimes every individual pair, seems to constitute a *casus sui*

generis."); W. Soudjin, "Advantages and Disadvantages in the Application of Bioactive Racemates or Specific Isomers as Drugs," *in Stereochemistry and Biological Activity of Drugs* 87, 100 (1983) (Def. Ex. 495) (noting the need for "extensive pharmacological, toxicological and clinical pharmacological research" to determine "whether it is advantageous to use racemates or enantiomers in clinical practice").

There are numerous drugs marketed as racemates in which there is no clear difference between the activities of stereoisomers, or where even though one enantiomer shows a greater level of activity, the drug is nonetheless marketed as a racemate. Dr. Thomas K. Harden, an expert for Sanofi, described fluoxetine, gatifloxacin, amphetamine, and sotalol as drugs in the latter category. (Harden Tr. 2306, 2310-15.) At the time that Sanofi decided to investigate the enantiomers of PCR 4099, Dr. Maffrand was aware that in some cases, the stereoisomers of a drug have greatly different activities (e.g., ibuprofen, thalidomide), but their metabolism *in vivo* – as opposed to *in vitro* – leads to racemization or interconversion to a different enantiomeric or achiral compound. (Maffrand PI Tr. 171-72.) Racemization is a process whereby a compound consisting of a single enantiomer is converted to a one-to-one mixture of that enantiomer and its opposite (i.e., the racemate) by the cleavage and reformation of a chemical bond at the chiral center of the molecule. (Davies Tr. 1956.) The Court finds that a person of ordinary skill in the art would also have been aware of these cases, and would have known that the risk of racemization in the body potentially eliminates any pharmacologi-

cal advantage derived from preparing the individual enantiomers. (Maffrand Tr. 1656-57.)

In addition, Sanofi's work on thienopyridines heightened Dr. Maffrand's uncertainty regarding the pharmacological potential of PCR 4099's enantiomers. Dr. Maffrand knew, for example, that thienopyridines were active only after administration to live animals, but were not active after *in vitro* exposure to isolated platelets. (Maffrand Tr. 1684-85; Harden Tr. 2325-26.) On that basis, Dr. Maffrand and his colleagues inferred that PCR 4099 required metabolic conversion – which takes place *in vivo* – to an active metabolite. (Maffrand Tr. 1684-85; Harden Tr. 2325-26; Snyder Tr. 586.) That active metabolite might not be chiral, and, even if chiral, its mechanism might not show stereoselectivity. (Maffrand Tr. 1685-86; Hanson Tr. 2213-14; Harden Tr. 2325-26; Snyder Tr. 585-86.) If so, this would mean that pursuing the enantiomers of PCR 4099 might have no benefit. This, in turn, would suggest that development efforts focus on the racemate instead of the enantiomers.

Furthermore, Sanofi's prior work on the enantiomers of racemic thienopyridine compounds did not suggest that the separated enantiomers would exhibit different types or levels of activity. (Maffrand Tr. 1696-1700). Although Sanofi had previously observed that only one of the enantiomers of PCR 1033 exhibited antiplatelet activity, the enantiomers of PCR 3549, by contrast, had exhibited equivalent levels of activity. (Maffrand 1598-99, 1604-05.) Furthermore, the Court credits Dr. Davies' testimony that a medicinal chemist would not expect PCR 1033 and PCR 4099 to behave in the same manner in the

body on the basis of any structural similarity; PCR 4099 has an ester group, which allows for significant hydrogen bonding, whereas PCR 1033 does not. (Davies Tr. 2009-14.) In sum – as experts from both parties agree – it was not possible to predict whether either enantiomer would be more or less therapeutically active – and more or less toxic – than the other. (Snyder Tr. 591-92; Davies Tr. 2014-16; McClelland PI Tr. 505-06.)

B. *Predicting Whether the Enantiomers of PCR 4099 Could Be Prepared*

In addition, Dr. Maffrand and his colleagues could not predict with any reasonable degree of certainty that they would be able to obtain the enantiomers of PCR 4099. Up until the decision to attempt the resolution of PCR 4099, Sanofi had only twice attempted – albeit successfully – to obtain the enantiomers of racemic thienopyridines, even though Sanofi had synthesized approximately 1500 thienopyridines, of which roughly 600 were racemates with chiral carbon atoms. (Maffrand Tr. 1618-19.) As of 1987, there were at least ten different methods by which a chemist could try to obtain the individual enantiomers of a chiral compound. (Davies Tr. 1921-22.) After choosing a particular technique, a chemist would also have to make numerous decisions: the choice of solvents, of reagents, of concentrations, of temperature, and of time. (Davies Tr. 1939-43.) Sanofi's expert Dr. Davies testified on direct examination that there is no way to predict which method or methods will succeed if no prior art deals with the compound at hand; practitioners will begin with a method with which they are familiar or a method for

which the necessary reagents are readily available.[5] (Davies Tr. 1939.)

As noted above, Sanofi had used diastereomeric salt formation to separate the enantiomers of PCR 1033, but had failed when trying to use that method to separate the enantiomers of PCR 3549. As of 1987, the prior art – including standard textbooks of organic chemistry – was replete with discussions of how to resolve enantiomers by diastereomeric salt formation, which was first identified by Louis Pasteur in 1853 and is sometimes referred to as "the classical method." (Davies Tr. 1925; Snyder Tr. 149-51, 155-56). The Feiser, Karrer, and Jacques references make clear that diastereomeric salt formation was a method of enantiomeric resolution that was well known in the art at the time that Sanofi chemists faced the task of obtaining the enantiomers of PCR 4099. *See* Louis F. Feiser & Mary Feiser, *Advanced Organic Chemistry* 85-89 (1961) (Def. Ex. 1322); Paul Karrer, *Organic Chemistry* 98-99 (1946) (Def. Ex. 162); Jean Jacques, et al., *Enantiomers, Racemates, and Resolutions*, 378-88 (1981) (Def. Ex. 492).

However, Dr. Davies explained that although that method is "one of the oldest methods," that does not mean that it is the best method, the easiest method to apply, or "the first one you should try." (Davies Tr. 1925-26.) As a general matter, obtaining the first crystals of any new compound through separation of diastereomeric salts is difficult. Jacques, for exam-

---

[5] On cross-examination Davies did concede that at least five of the methods available would have been identified as inappropriate in the case of PCR 4099. (Davies Tr. 2023-24.)

ple, teaches that "[n]o infallible recipe exists for overcoming the resistance of a diastereomer to crystallize for the first time." (Jacques (Def. Ex. 492) at 386.) The Eliel reference confirms this point:

> Unfortunately, resolution is, in this respect, still very much a matter of trial and error, and even in the papers of experienced investigators one is apt to find, from time to time, a statement that a certain compound resisted resolution by any one of a large number of combinations of resolving agents and solvents that were tried.

Ernest L. Eliel, *Stereochemistry of Carbon Compounds* 50 (1962) (Def. Ex. 1930). *See also* McClelland Tr. 1117-21; Davies Tr. 1945-48. Although screening techniques would have allowed a person of ordinary skill in the art to improve the odds of a successful separation, diastereomeric salt separation was – and remains even today – a "paradigm of trial and error." Ton Vries, et al., "The Family Approach to the Resolution Of Racemates," *J. Angewandte Chemie* 2349 (1998) (Pl. Ex. 852); *see also* Jacques, Def. Ex. 492 at 380; McClelland Tr. 1137-39. Experts from both parties agreed that although a chemist can search the prior art for useful examples of prior resolutions of similar compounds, the precedents afford absolutely no assurance that the same configuration will succeed with a different compound. (McClelland Tr. 1118; Davies Tr. 1975; *see also* Eliel (Def. Ex. 1930) at 50.) Furthermore, the literature tends not to report failed resolution attempts. (McClelland Tr. 1135.) In the particular case of PCR 4099, the prior art offered no examples of the resolutions of chiral thienopyridines, and Apotex's

expert Dr. McClelland – in preparing for his testimony – did not find *any* reference that contained the set of conditions that Sanofi ultimately used to obtain the enantiomers of PCR 4099. (McClelland Tr. 1071.) In fact, Dr. McClelland did not find any relevant instances of the resolution of thienopyridines in the prior art. (McClelland Tr. 1127; 1230-32.)

In addition, a person of ordinary skill in the art would have recognized the possibility that it would be more difficult to prepare the enantiomers of PCR 4099 than it had been to prepare the enantiomers of PCR 1033 and PCR 3549. First, the meythl ester group attached to the chiral center in PCR 4099 made that molecule more susceptible than PCR 3549 to racemization. (Hendrickson Tr. 1498; Maffrand Tr. 1656, 1700; Badorc Tr. 1832-33.) Indeed, a person of ordinary skill in the art would have known that phenylglycine and its derivatives – of which PCR 4099 is one – are susceptible to racemization. (Badorc Tr. 1832; Davies Tr. 1956-60.) Second, because of the presence of the ester substituent on PCR 4099, the hydrogen atom located on the chiral carbon could easily be removed through the action of a base or an acid (which would be required in the course of resolution of the enantiomers). A free hydrogen in solution could then reform a bond to the same carbon atom, but it would bond on either side of that atom with equal likelihood, thereby yielding a racemate. (Davies Tr. 1958-61; 2002-04.) Third, the enantiomers of PCR 4099 would be susceptible to racemization in the acidic environment of the stomach by the same mechanism. (Davies Tr. 2004; Hendrickson Tr. 1463.)

Accordingly, neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration.

C. *Resolution of the Enantiomers of PCR 4099*

In November 1985, Alain Badorc and Dr. Daniel Fréhel were asked to attempt to obtain the enantiomers of PCR 4099 in order to test whether either enantiomer would make a better drug than the racemate. (Maffrand Tr. 1650-51.) As the outset, Badorc and Dr. Fréhel decided not to attempt resolution through the formation of diastereomeric salts. The Court credits Badorc's testimony that that decision was influenced by the fact that PCR 4099 was "only barely basic and, therefore, only barely capable of carrying out a separation using diastereomeric salts." (Badorc Tr. 1829.) In addition, Badorc believed that there were few commercially available acids that were likely to form diastereomeric salts in sufficient quantities to permit resolution. (Badorc Tr. 1830.) Instead of attempting diastereomeric salt separation, Badorc decided to attempt chemical asymmetric synthesis, the method that he had successfully used to prepare the enantiomers of PCR 3549. This choice was facilitated by the commercial availability of the required starting materials. (Badorc Tr. 1829-31.)

Badorc's lab notebook and a June 12, 1986 report show that Badorc reacted the starting materials to form the enantiomers of an intermediate compound –

referred to as "OCBATH." (Pl. Ex. 50.) He then used the same "reaction sequence" that he had used in the synthesis of the enantiomers of PCR 3549. (Hendrickson 1497-98; Badorc 1836-37; Pl. Ex. 50 at S 03977-78; Pl. Ex. 51 at S 58990-91.) With PCR 4099, however, the sequence failed because the second reaction in the sequence, a condensation, yielded a racemic form of the desired product, not a pure enantiomer. (Badorc Tr. 1836-37; Pl. Ex. 50 at S 03978; Pl. Ex. 51 at S 58991.)

Badorc then tried a different approach. Starting from the racemic OCBATH, he attempted to separate that intermediate's enantiomers through the formation of diastereomeric salts with tartaric acid in isopropanol. After several crystallizations, Badorc obtained enantiomers with the same melting point and equivalent levels of optical rotation. (Badorc Tr. 1837-38; Pl. Ex. 50 at S 0379-80; Pl. Ex. 51 at S 58992-93.) Badorc then attempted to convert the enantiomers of OCBATH into those of PCR 4099 using the same cyclization reaction conditions used to prepare the enantiomers of PCR 3549. That product, however, also racemized. (Badorc Tr. 1838; Pl. Ex. 50 at S 03980; Pl. Ex. 51 at S 58993.)

Badorc also tried using diastereomeric salts to resolve the enantiomers of the acid precursor of PCR 4099, a compound designated as PCR 3068. To that end, he attempted resolution with several different chiral bases, but those efforts failed because no crystals formed. (Badorc Tr. 1839-42; Pl. Ex. 50 at S 03891.) When Badorc attempted to form diastereomeric salts of PCR 3068 with chirally pure d-camphorsulfonic acid in ethanol, crystals did form, but that effort failed because the crystals contained

salts of both enantiomers, rather than just of one. (Badorc Tr. 1841-42.)

At that point – in January 1986 – Badorc revisited the technique that he had originally been reluctant to use and attempted to resolve the enantiomers of PCR 4099 directly by diastereomeric salt formation. (Badorc Tr. 1842.) To determine what combination of acid, solvent, and concentration would yield crystals, Badorc set up a "screening" experiment with approximately thirty test tubes containing various combinations of a chiral acid (e.g., camphorsulfonic, toluoyltartaric, dibenzoyl tartaric, mandelic, and tartaric) with PCR 4099 in various concentrations and in various solvents. (Badorc Tr. 1842-43.) Badorc obtained a solid material in only one of the test tubes – a gummy substance at the bottom of the tube containing a 1:1 ratio of camphorsulfonic acid and PCR 4099 in acetone. (Badorc Tr. 1844.) No crystals were obtained in any test tube. (Badorc Tr. 1844.)

In mid-February, Badorc began an additional screening test of several test tubes with different combinations of acid, solvent, and concentration. (Badorc Tr. 1844-45.) Badorc checked the test tubes each day for crystals, the presence of which would indicate the formation of a potentially separable diastereomeric salt. (Badorc Tr. 1846.) Approximately one month after beginning the experiment, Badorc detected crystals in only one tube – the tube that contained (+) camphorsulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone.[6] (Badorc Tr. 1846-

---

[6] Dr. Robert A. McClelland, an expert for Apotex, testified that each recrystallization takes from four hours to "perhaps

47.) As noted above, that same combination using the acid and PCR 4099 in a 1:1 ratio had not yielded crystals. (Badorc Tr. 1843-44.)

Because the small test tube reaction had not yielded a sufficient quantity of crystals for further testing, Badorc carried out a larger version of the experiment on March 18, 1986. (Badorc Tr. 1847-48; Pl. Ex. 72 at S 02014.) Risking the loss of the crystals that he had obtained, Badorc used those crystals to seed the larger version, which – after several trials – yielded a significant quantity of crystals of the levorotatory enantiomer of PCR 4099 in the camphorsulfanate form. (Badorc Tr. 1848-49; Pl. Ex. 72 at S 02014.) Using the same conditions – but substituting chirally pure 10-camphorsulfonic acid of opposite rotation – Badorc also resolved the dextrorotatory enantiomer (i.e., clopidogrel). (Badorc Tr. 1850-51; Pl. Ex. 50 at S 03986; Pl. Ex. 74 at S 02019.) Finally, to form the free base of both resolved enantiomers, Badorc reacted the camphorsulfonate salt forms with sodium bicarbonate, a base. (Badorc Tr. 1852.) Badorc verified the optical purity of the free base compounds to confirm that he had resolved the enantiomers and that they had not racemized at any stage. (Badorc Tr. 1852-53.) Nothing in the prior art – and nothing in his own experience with PCR 1033

---

overnight," and that a person of ordinary skill in the art would generally wait only that long, or "maybe for a few days," to see if crystals will form. (McClelland Tr. 880, 1131.) However, in the case of Badorc's second test tube screening experiment, it took approximately *one month* for crystals to form. (Badorc Tr. 1846.) The disparity between Dr. McClelland's testimony and the factual record undermines the proposition advanced by Apotex that the resolution of the enantiomers of PCR 4099 was a simple, routine procedure.

and PCR 3549 – directed Badorc to employ the precise configuration of acid, solvent, and concentration that was ultimately successful with PCR 4099.

D. *Preparation of Clopidogrel as a Pharmaceutically Acceptable Salt*

To permit the testing and comparison of the properties of the enantiomers of PCR 4099 to those of the racemate, which had only been tested as a hydrochloride salt, Badorc prepared the hydrochloride salts of each enantiomer. (Badorc Tr. 1852-53.) As described below, pharmacological and toxicological testing showed that clopidogrel hydrochloride exhibited more antiplatelet activity than PCR 4099 and was better tolerated than the l-enantiomer, but – as a hydrochloride salt – the compound was hygroscopic (i.e., it had a tendency to absorb water from the atmosphere) and lacked stability. (Badorc Tr. 1853; Banker Tr. 1338; Pl. Ex. 48 at S 03781.) This made it a poor candidate for commercial tablet manufacture. For that reason, during May and June of 1987, Badorc searched for a salt form of clopidogrel that would be more suitable for use in commercial tablets. (Badorc Tr. 1854.)

Salts are formed by mixing an acid with a base. (Banker 1274, 1299-1300.) A basic rule of salt formation is that a weak base – such as PCR 4099 – generally requires a strong acid to form a salt.[7] (Banker 1274, 1300.) A measure of the strength of an

---

[7] In addition to selecting the acid, the chemist must also choose a solvent and co-solvent in which to attempt to precipitate the crystals, and must also consider temperature and cooling rates. (Byrn Tr. 2127-29.)

acid or a base is its "pKa": a low pKa signifies a strong acid and a high pKa signifies a weak acid. (Banker 1274; Byrn Tr. 2111-12.) In 1977 and 1986, the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds and twenty-one bases as candidates for forming salts with acidic compounds. On this point, the Court credits the Berge reference and the Gould reference. *See* Stephen M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1, 2-3 (1977) (Pl. Ex. 152); Philip L. Gould, "Salt Selection for Basic Dugs," 33 *Int'l J. Pharm.* 201, 202, 214-16 (1986) (Pl. Ex. 153); Byrn Tr. 2126. Of the eighty acids listed by Berge, fifty-three were used in FDA-approved drugs as of 1974; the remaining twenty-seven were commercially marketed in other countries. (Berge (Pl. Ex. 152) at 2-3; Byrn Tr. 2126.) The Berge reference also taught the pKa of each of those acids. (Berge (Pl. Ex. 152) at 2-3.)

If the difference in pKa of an acid and base is greater than two, the "delta pKa rule" is a guideline that suggests that the amount of salt present in solution – as compared to that of the unreacted acid and base – will be greater than if the difference in pKa is less than two. (Byrn Tr. 2112-15.) However, even if the pKa difference between an acid and a base is only one or zero, their reaction will still yield a 10:1 or 1:1 ratio, respectively, of protonated to unprotonated base in solution. (Davies Tr. 2064-65; Byrn Tr. 2114-16.) The presence of protonated base will, in turn, permit salt formation in solution, from which crystals of the salt might precipitate. (Davies Tr. 2064-65; Byrn Tr. 2114-16.) For that reason, a person of ordinary skill in the art would not necessarily

have excluded from consideration those acids whose pKa values differed from that of the relevant base by less than two. (Davies Tr. 2065; Byrn Tr. 2115-16.) Weak acids – where the resulting pKa difference is less than two – might even be preferable where there is the risk of acid-catalyzed racemization or hydrolysis of the base. (Byrn Tr. 2119.) Therefore, a person of ordinary skill in the art would not be able to predict from the list provided by Berge which acids would form useful salts for drug purposes. (McClelland PI Tr. 503-04.)

Depending on their properties, salts of pharmaceutical compounds can be characterized according to three general types, or "tiers." (Byrn Tr. 2109-11.) A Tier 1 salt results from the simple reaction of an acid and a base in solution, without regard to its properties. (Byrn Tr. 2109-10.) A Tier 2 salt is a solid salt that facilitates testing, but may be hygroscopic or unstable over the long term and, for either of those reasons, may not be suitable for use in tablets. (Byrn Tr. 2110.) A Tier 3 salt – the type of salt that is generally desirable for use in a drug tablet – is crystalline, non-hygroscopic, stable as a tablet, soluble in bodily fluids, dissolved fast enough to allow absorption in the body, not sticky, and without a static charge. (Byrn Tr. 2110-11, 2120-21; McClelland Tr. 1173-74.)

Formation of a crystalline salt is important for an orally administered drug such as clopidogrel, and the salt form of a drug can affect a drug's pharmacological properties because of its effect on solubility, which influences absorption in the body and bioavailability. However, the prior art teaches – and both parties' experts agreed and the Court finds –

that whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable. (McClelland PI Tr. 503-04; McClelland Tr. 1101-02; Snyder Tr. 544-45; Byrn Tr. 2122-23.) In particular, Berge taught that:

> Choosing the appropriate salt . . . can be a very difficult task, since each salt imparts unique properties to the parent compound . . . Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound.

Berge (Pl. Ex. 152) at 1. Making reference to Berge, the Gould publication provided similar teaching nearly a decade later:

> The importance of choosing the 'correct' salt form of a drug is well outlined in a published review (Berge et al., 1977) but, although salt form can have a dramatic influence on the overall properties of a drug, the selection of the salt form that exhibits the desired combination of properties remains a difficult semi-empirical choice.

Gould (Pl. Ex. 153) at 201. In addition to this high level of general unpredictability, a person of ordinary skill in the art would have recognized that there is no correlation between a racemate and its corresponding enantiomers when it comes to making a crystalline salt. (Banker Tr. 1322-24; Davies Tr. 1955-56; Byrn Tr. 2123-25.) The physical properties of racemates and their enantiomers, as well as of

their respective salts, differ because the molecules pack differently, leading to different crystal structures. (Snyder Tr. 543-45; Banker Tr. 1321-23, 1327; Davies Tr. 1955; Byrn Tr. 2123-2125.) In other words, the salt form of a racemate may produce a very different crystalline structure than the same salt forms of the enantiomers of that racemate. For that reason, even if a person of ordinary skill in the art looking at the '596 patent had concluded that PCR 4099 should be reformulated as a bisulfate salt, that would not imply that the enantiomers of PCR 4099 – if obtained – should also be prepared as bisulfate salts. (Davies Tr. 1914-15; Byrn Tr. 2136-38.) Accordingly, there would have been no way for a person of ordinary skill in the art to deduce from the examples of the '596 patent that clopidogrel would form a bisulfate salt and that it would be a Tier 3 crystalline salt. (Davies Tr. 1915; Byrn Tr. 2136.)

Tasked with identifying a suitable crystalline, non-hydrochloride salt of a drug, a person of ordinary skill in the art would look to the approximately fifty pharmaceutically acceptable (i.e. FDA-approved) acids identified by the prior art. (McClelland PI Tr. 490-91; Byrn Tr. 2126.) This was essentially the approach taken at Sanofi, where Badorc and his colleagues reacted clopidogrel with an array of approximately twenty-one different acids – only about ten of which were strong acids – in different solvents. (Badorc Tr. 1854-55; Maffrand 1773-74; Pl. Ex. 73 at S 02245, S 02248-60, S 02276; Pl. Ex. 74 at S 02054.) Badorc used both strong and weak acids because it was not possible to predict which acid would yield a crystalline salt meeting all of the criteria for a suitable pharmaceutical tablet. (Badorc Tr. 1854-55;

Byrn Tr. 2140-46.) When Badorc attempted to create the sulfate form of clopidogrel, the reaction instead resulted in its bisulfate salt. (Badorc Tr. 1797-98.) Although sulfuric acid was one of the first acids that he tried, Badorc continued to test other acids. (Badorc Tr. 1854-55; McClelland Tr. 2565.) This was not unreasonable. On the contrary, it would have been reasonable for a person of ordinary skill in the art to try a variety of weak acids and strong acids so as not to overlook potential Tier 3 salts. (Badorc Tr. 1854-55; Davies Tr. 1969-70; Byrn Tr. 2144-46.)

The bisulfate salt proved to be the only salt with the optimal properties: a high melting point, long-term stability, non-hygroscopicity, and good solubility. (Badorc Tr. 1855; Banker Tr. 1357.) Although a person of ordinary skill in the art would have known that hydrochloric acid, hydrobromic acid, and sulfuric acid were the three strongest acids used in pharmaceutical salts, a person of ordinary skill in the art would not have reasonably expected the bisulfate salt of clopidogrel to have the highly favorable combination of properties that it turned out to possess. (Byrn Tr. 2164.) First, the highly acidic nature of the bisulfate posed a significant risk of racemization, which made it unattractive for use with an enantiomeric compound. (Byrn Tr. 2158; Davies Tr. 1970-72.) Second, the Court credits the testimony from Dr. Stephen R. Byrn, an expert for Sanofi in the area of solid state chemistry, that the relevant prior art not only provided no positive indication that sulfuric acid would lead to a successful crystalline salt, but the prior art in fact would have led a person of ordinary skill in the art away from sulfuric acid in the case of clopidogrel. (Byrn Tr. 2160-63.) Specifically, the

Gould publication taught that to avoid hygroscopicity – the problem posed by the hydrochloride salt of clopidogrel – one should avoid polar salts, which would include the bisulfate. (Gould (Pl. Ex. 153) at 210-13; Byrn Tr. 2158-59, 2162.) Instead, Gould pointed to the use of carboxylic acids, which, in the case of clopidogrel, proved unsuccessful. (Gould (Pl. Ex. 153) at 210-13; Byrn Tr. 2160-63.) Third, another prior art reference – the Berge publication – did not even list the bisulfate salt in its list of FDA-approved commercially marketed salts; the bisulfate appears only on the list of non-FDA approved salts, making it all the more surprising that the bisulfate salt of clopidogrel, in fact, proved to be a highly suitable pharmaceutical formulation. (Berge (Pl. Ex. 152) at 2-3; McClelland PI Tr. 491.) For all of these reasons, a person of ordinary skill in the art could not have reasonably expected that the bisulfate salt of clopidogrel would be the optimal pharmaceutical salt form of the compound.

V. *The Biological Properties of Clopidogrel*

A. *The Pharmacological Properties of the Enantiomers of PCR 4099*

Testing demonstrated that the dextrorotatory enantiomer – clopidogrel – exhibited good platelet inhibition activity. (Maffrand Tr. 1659.) By contrast, the levorotatory enantiomer was "completely ineffective"; it showed no statistically significant activity in any assay. (Maffrand Tr. 1659; Snyder Tr. 2526-29.) This absolute stereoselectivity of platelet inhibition for the enantiomers of PCR 4099 was unexpected in light of the prior art. (Davies Tr. 2014-

15, 2018-19; Hanson Tr. 2214, 2216, 2250-51; Harden Tr. 2338.)

A finding that the absolute stereoselectivity of the enantiomers of PCR 4099 was unexpected was not undermined by the prior art regarding ADP platelet receptors, including the work of Dr. Robert Colman, a platelet physiologist. Apotex has failed to persuade the Court that Colman's work – in particular, a 1984 article co-authored by Colman – would have made Sanofi's results unsurprising to a person of ordinary skill in the art. *See* Robert W. Colman & William R. Figures, "Characteristics of an ADP receptor mediating platelet activation," *Molecular & Cellular Biochem.* 101 (1984) (Def. Ex. 519). As of 1987, platelet physiologists suspected the existence of one or more platelet receptors for ADP, and they knew that the suspected receptors were stereoselective for the naturally occurring stereoisomer of ADP. (Hanson Tr. 2216-17; Harden Tr. 2321-22.) Based on that phenomenon, however, a person of ordinary skill in the art would not have drawn the inference that chiral antagonists would inhibit platelet activation stereoselectively. (Hanson Tr. 2217-18; Harden Tr. 2322-23.) In the early 1980s, Dr. Colman identified a protein on the surface of platelets – aggregin – that he posited was a receptor for ADP. (Colman Tr. 1015-20.) Dr. Colman's work did not, however, address whether thienopyridines inhibited platelet activation through interaction with aggregin or any other protein – his work in the 1980s did not involve thienopyridines. (Snyder Tr. 605-06; Colman Tr. 1024-25; Maffrand Tr. 1676-77.) Nor did Dr. Colman's work address whether aggregin interacted with any molecule in a stereoselective fashion; he did

not compare the effects of different stereoisomers of the same chiral molecule on aggregin or platelet activation. (Harden Tr. 2334-35; Snyder 605.) Thus while Colman's work, including the 1984 article, relates generally to the problem of platelet aggregation that Sanofi's research also addressed, the 1984 article was of no particular significance to the properties that Sanofi discovered clopidogrel to possess.

B. *The Toxicological Properties of the Enantiomers of PCR 4099*

Sanofi also subjected the enantiomers of PCR 4099 to a battery of toxicological testing. In acute toxicity testing of PCR 4099 and its enantiomers in March 1987, Sanofi calculated the doses at which each of the compounds is lethal in rats. The tests – reported internally in a research memorandum dated May 18, 1987 – showed that the LD_{50} for clopidogrel (4316 mg/kg) was much higher than the LD_{50} of either PCR 4099 (1615 mg/kg) or the l-enantiomer (1702 mg/kg).[8] (Lacheretz Tr. 2377-79; Pl. Ex. 118 at 11.) This showed that the acute toxicity of the levorotary enantiomer and PCR 4099 was "very different" – i.e., significantly higher – than that of clopidogrel. (Lacheretz Tr. 2379.) The absolute lethal doses of PCR 4099 and the levorotatory enantiomer were similar (2000 mg/kg) and were also lower than the absolute lethal dose of clopidogrel (5000 mg/kg). (Maffrand Tr. 1688-89; Pl. Ex.118 at 2.) Furthermore, convulsions were observed in animals

---

[8] The LD_{50} is the calculated dose of a compound at which 50 percent of the test animals administered the compound die. Similarly, the LD_{10} indicates the single dose at which 10 percent of the animals tested die. (Lecheretz Tr. 2358.)

receiving PCR 4099 and the l-enantiomer in a comparative acute toxicity study, but no convulsions were observed in animals receiving clopidogrel, including clopidogrel in any of its hydrochloride, bisulfate, or hydrobromide forms. (Lacheretz Tr. 2377; Pl. Ex. 130.) In sum, the data collected from tests conducted by Sanofi – data which was later reported in the '265 patent – showed (1) that the levorotatory enantiomer is lethal at significantly lower doses than clopidogrel, and (2) that the levorotatory enantiomer is neurotoxic, but clopidogrel is not. (Graham Tr. 2423-24; Maffrand Tr. 1688-90; Lacheretz Tr. 2387.) According to Sanofi's toxicologist Dr. Lecheretz, Sanofi concluded from these results that clopidogrel was "much less toxic or, in other terms, much better tolerated" than both the levorotatory enantiomer and PCR 4099. (Lacheretz Tr. 2380.)

That conclusion was amply supported at trial. Dr. Joseph V. Rodricks, an expert for Sanofi, explained that a drug's therapeutic index is a measure of a drug's safety and is calculated based on the ratio of its toxic dose to the dose that "reflects efficacy," i.e., the dose that has a therapeutic effect. (Rodricks Tr. 2488.) A higher therapeutic index indicates a safer drug. (Rodricks Tr. 2488-90.) Based on data from short-term studies, Dr. Rodricks testified that clopidogrel has a much higher therapeutic index than PCR 4099, which indicates clopidogrel's safety advantage over the racemate. (Rodricks Tr. 2494-95.) Based on data derived from longer-term studies, Dr. Rodricks determined that PCR 4099's low therapeutic index demonstrates a valid safety concern. (Rodricks Tr. 2496-99.) In contrast, serious toxic

effects were not observed in response to any dose of clopidogrel in the longer-term studies. (Rodricks Tr. 2495-98.)

Based on the documentary evidence and testimony relating to both the pharmacological and toxicological properties of clopidogrel, the Court finds that the prior art offered no basis to reasonably expect that the resolution of PCR 4099 would yield an inactive enantiomer that was also less well-tolerated than the active enantiomer. (McClelland PI Tr. 505-06; Snyder Tr. 591-92; Harden Tr. 2250-51.) Accordingly – and most importantly – the fact that clopidogrel was both the more active enantiomer of PCR 4099 *and* was better tolerated than the levorotatory enantiomer would have been unexpected to a person of ordinary skill in the art prior to obtaining the separate enantiomers and testing them.

C. *Sanofi's Decision to Discontinue Development of PCR 4099*

In March 1987, Pierre Simon, then the head of research and development at Sanofi, reviewed the pharmacological and toxicological studies of PCR 4099 and its enantiomers. At that time, Dr. Maffrand was reluctant to discontinue the development of PCR 4099 in favor of clopidogrel. (Maffrand PI Tr. 154.) In an internal memorandum dated March 31, 1987, Dr. Maffrand noted that tests had shown PCR 4099 to be "consistently active in healthy volunteers," but that it had been "consistently ineffective in patients" for reasons yet unknown. (Def. Ex. 622.) Maffrand further noted that the active enantiomer of PCR 4099 showed less acute toxicity in rats and mice than the inactive enantiomer, but that there was not yet data

available on subacute toxicity. (*Id.*) Nonetheless, Dr. Maffrand expressed doubts about abandoning Sanofi's work on PCR 4099 in favor of the active enantiomer, noting that "[i]t isn't the inactive enantiomer that is causing the problems with PCR 4099 we are encountering today." (*Id.*) At the preliminary injunction hearing, Dr. Maffrand testified that by that time, Sanofi had performed more than fifty tests on PCR 4099 from 1980 to 1987, including phase I human trials, at a cost of "tens of millions of dollars." (Maffrand PI Tr. 143-44, 152-53.) To develop clopidogrel, Sanofi would not have been able to rely on the data from tests that related to PCR 4099. As a result, Dr. Maffrand at that time viewed switching to the development of the active enantiomer instead of the racemate as a four year setback. (Maffrand PI Tr. 155.)

Nonetheless, Simon decided to terminate the development of PCR 4099 in favor of focusing on clopidogrel. (Maffrand Tr. 1666.) In an April 16, 1987 internal memorandum setting forth his decision, Simon wrote the following:

> These studies have demonstrated that only the D form is active and that, moreover, the L form was more toxic and was specifically responsible for convulsions observed in animals at high doses. Under these conditions, it appears clear to me that we cannot envision development of the [racemate], and I have decided to stop this development. Our efforts therefore are turning to the D form and we are taking all possible steps to reduce lost time to a minimum.

(Pl. Ex. 57t.) Accordingly, the development of PCR 4099 was stopped.

On November 6, 1987, Sanofi held a meeting in Japan with its partners in a joint venture. That meeting included discussion of the decision to abandon PCR 4099. A memorandum describing the meeting suggests that the reason for discontinuing the development of PCR 4099 in favor of clopidogrel was based on Sanofi's discovery that the therapeutic activity was located only in the dextrorotatory enantiomer and that "the [l-enantiomer] is more toxic than the [d-enantiomer] qualitatively and quantitatively." (Def. Ex. 13.) Moreover, the memorandum also notes the following:

> The trend in regulatory requirements would have made it difficult to get the NDA approval with the racemic either in France or in Europe or in the United States. It is the reason why SANOFI stopped the development of PCR 4099. In any case, our decision was not due to problem[s] in preclinical or in clinical studies, particularly no problem of G.I. intolerance was noted in volunteers, showing an advantage over Ticlopidine. For Japan, it also seems that it would not have been possible to apply for a NDA with the racemic in such a case.

(*Id.*) Nonetheless, because the November 7, 1987 meeting took place several months after Simon's April 16, 1987 memorandum – which focused specifically on the neurotoxicity problems associated with PCR 4099 – and, more generally, well after Sanofi had decided to split the enantiomers of PCR 4099, the Court credits the extensive trial testimony and

documentary evidence that the decision to discontinue the development of PCR 4099 in favor of clopidogrel was based on the sub-optimal side effect profile of PCR 4099, not because of any specific concern raised by Sanofi's joint venture partner or any nascent regulatory trend mandating the investigation of enantiomers where a racemic drug was proposed.

VI. *The '265 Patent*

A. *The French Patent*

As described above, Sanofi applied for a French patent claiming clopidogrel and its salts on February 17, 1987 – at a time when Sanofi was still actively engaged in developing PCR 4099. Prior to filing the application, Fréhel put together an initial draft of that application, which he circulated on December 1, 1986. That draft included the following statement in the specification: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Exs. 8 at S 91129, 425 at S 91129.) That statement was based on observations made by Sanofi scientists in the course of pharmacological testing of the enantiomers of PCR 4099. (Maffrand Tr. 1659-64.) That statement remained in the version of the application that was submitted to the French regulator, and, eventually, to the PTO in the United States.

On December 30, 1986, after Fréhel's initial draft had been circulated internally, Michel de Haas, head of Sanofi's legal department, circulated a memo with

the heading "Patentability of the two enantiomers of PCR 4099." In that memo, Haas wrote:

> [I]f we ever develop the active isomer [i.e., clopidogrel], it would be very useful to have a patent for this isomer (prolonging our monopoly, prohibiting its use by third parties in countries where [PCR] 4099 is not patented as a product . . .). Issuing such a patent will only be effective, at least in countries with an examination process, if we make mention of an 'unexpected' advantage (whether this is the reason for developing the product or not).

(Def. Ex. 628.) Haas also noted that Sanofi would not develop the active enantiomer if it showed "no major therapeutic advantage" over PCR 4099 considering the cost of manufacture, either "by stereospecific synthesis or by separation from the racemic." (*Id.*) In the alternative, Haas noted that they might find the active enantiomer "very attractive" if, for example, "it does not have . . . some of the objectionable side effects of PCR 4099 (bleeding . . .)." (*Id.*)

In late January 1987, Jacqueline LaForest, an in-house French patent attorney at Sanofi, reviewed Fréhel's draft application for the French patent. (Maffrand Tr. 1673.) Although LaForest had studied chemical engineering as an undergraduate student, she did not have training in pharmacology or toxicology. (Maffrand Tr. 1673.) In comments dated January 26, 2007 to the draft application, LaForest wrote: "[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner's hurdles without other results." (Def. Ex. 304.) Laforest also wrote: "If I understood the text [of the application]

correctly, PRP aggregation results [i.e., results of testing of the compounds' ability to inhibit platelet aggregation] are missing . . . ." (*Id.*) However, those very results in fact appeared prominently in the application that Laforest was reviewing. (Snyder Tr. 645-46; Maffrand Tr. 1674; Def. Ex. 304.) Furthermore, LaForest's written comment on the lack of "surprising activity" was made before the results of subsequent March 1987 toxicology studies were known. (Maffrand PI Tr. 152.)

B. The U.S. Patent

On February 12, 1988, Sanofi filed an application in the United States for a patent on clopidogrel and certain of its salts. The U.S. application, as had the French application, contained the statement: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Ex. 9 at CLO-DRL 51362.)

In support of that statement, Sanofi's application reported the results of three different pharmacological tests and one acute toxicity test. The acute toxicity test showed that clopidogrel was lethal at doses that were double those at which the levorotatory enantiomer and the racemate were lethal. (*Id.* at CLO-DRL 51379-80.) This demonstrated that clopidogrel was much less toxic than the levorotatory enantiomer. (Maffrand PI Tr. 251-53; Maffrand Tr. 1688-89; Graham Tr. 2424.) In addition, between the dates that Sanofi filed the French patent application and the U.S. patent application, Sanofi scientists had

conducted additional toxicological tests, the results of which – as described above – demonstrated that the levorotatory enantiomer and PCR 4099 caused convulsions at doses which clopidogrel did not. (Maffrand PI Tr. 151-52.)

The examiner of the application for the '265 patent was Bernard L. Dentz, the same examiner who had approved the '596 patent. On November 4, 1988, Dentz initially rejected Claims 1-5 and Claims 10-11 as unpatentable because he believed the disclosure of PCR 4099 in the '596 patent anticipated them. (Fact Stmt. ¶ 21.) In the rejection, however, Dentz stated that Sanofi could correct its application by adding the limitation "substantially pure" as a means of distinguishing the claims of the '265 patent from the claims of the '596 patent. (*Id.*) Dentz also noted that if Sanofi made that amendment, a basis for the invention's patentability was Sanofi's reported data showing that the "toxicity" of the l-enantiomer "is markedly higher" than that of the d-enantiomer. (*Id.*)

On January 9, 1989, Sanofi amended claims 1-5 by inserting the phrase "substantially separated from the levo-rotatory isomer." (*Id.* ¶ 23.) On January 30, 1989, the PTO issued a Notice of Allowability for the amended claims. (*Id.* ¶ 26.) The '265 patent issued on July 11, 1989. (*Id.*)

C. The Clinical Application of Clopidogrel Bisulfate

Prior to the introduction of Plavix®, physicians prescribed aspirin and/or ticlopidine to prevent cardiovascular conditions believed to be caused or exacerbated by platelet aggregation. (Schneller Tr. 738-41.) The long-term use of aspirin is associated

with certain side effects, such as ulcers and gastrointestinal bleeding, and ticlopidine, as described above, is associated with an elevated risk of neutropenia and TTP. (Maffrand Tr. 1693-94; Schneller Tr. 763, 811-16.) Following its launch in 1998, Plavix® replaced ticlopidine as a prescription oral antiplatelet medication to a nearly complete extent. (Maffrand PI Tr. 155; Schneller Tr. 762, 806-07.)

Both prior to and since the launch of Plavix® on the market, large-scale clinical studies have been conducted involving clopidogrel. The results of the CAPRIE trial, published in 1996, showed that the long-term administration of Plavix® to patients with atherosclerotic vascular disease was more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or death caused by blockage of an artery. (Schneller Tr. 821-22.) Apotex's expert Dr. Stanley J.Schneller, a cardiologist, characterized the difference in efficacy as, however, "very modest." (Schneller Tr. 822.) CAPRIE also showed that Plavix® was associated with a low rate of neutropenia and TTP: only 0.1 percent of patients taking clopidogrel experienced neutropenia, and only 0.08 percent experienced neutropenia that was severe; no patient in the CAPRIE trial experienced TTP. (Schneller Tr. 812-817.) Dr. Schneller cautioned, however, that CAPRIE did not directly compare clopidogrel to ticlopidine; data derived from the CAPRIE study – when compared against historical data on ticlopidine – indicated a lower incidence of neutropenia and TTP with clopidogrel. (Schneller Tr. 812-13.)

Additional studies involving Plavix® included the CURE trial and the CLASSICS trial. The CURE trial, conducted between 1998 and 2000, demonstrated an 18.4% relative reduction in the risk of death, nonfatal myocardial infarction, or stroke in patients taking the combination of clopidogrel and aspirin versus patients taking aspirin alone. (Schneller Tr. 825.) Plavix® is also widely prescribed for patients who have received stents, the thin wire coils used to prop open arteries narrowed by arteriosclerotic plaque, to prevent thromboses that may form on the stents after their insertion. (Schneller Tr. 807-08, 811.) The CLASSICS trial demonstrated the superior safety of Plavix® compared to ticlopidine for stenting.

CONCLUSIONS OF LAW

I. *Infringement*

The parties have stipulated that Apotex's generic clopidogrel bisulfate product infringes Claim 3 of the '265 patent. That patent claims the "[h]ydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer," also known as clopidogrel bisulfate. ('265 patent at col. 12, ll. 37-41; *see also* Fact Stmt. at ¶¶ 18-19; May 7, 2004 Stipulation and Order.)

II. *Invalidity*

Having conceded infringement, Apotex bears the burden of proof because "[a] patent shall be presumed valid," and "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on

the party asserting such invalidity." 35 U.S.C. § 282. To overcome this presumption of validity at trial, "the party challenging a patent must prove facts supporting a determination of invalidity by clear and convincing evidence." *Schumer v. Lab. Computer Sys.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002) (citing *Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031, 1036 (Fed. Cir. 2001), *cert. denied*, 534 U.S. 1172, 122 S. Ct. 1196, 152 L. Ed. 2d 136 (2002)). As noted above, Apotex challenges the validity of the '265 patent on the grounds of anticipation, obviousness, and obviousness-type double patenting and challenges the enforceability of the '265 patent on the grounds that Sanofi engaged in inequitable conduct before the PTO. At trial, Apotex bore the burden of proving each of these defenses by clear and convincing evidence. *See Oney v. Ratliff*, 182 F.3d 893, 895 (Fed.Cir.1999) (invalidity); *Elk Corp. v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed.Cir.1999) (unenforceability), *cert. denied*, 528 U.S. 873, 120 S. Ct. 178, 145 L. Ed. 2d 150 (1999). This is a "heavy burden," *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (quoting *Radio Corp. of Am. v. Radio Eng'g Labs.*, 293 U.S. 1, 8, 54 S. Ct. 752, 79 L. Ed. 163 (1934)), because clear and convincing evidence "proves in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions [is] highly probable.'" *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S. Ct. 2433, 81 L. Ed. 2d 247 (1984)).

A. *Anticipation*

1. *Legal standard*

An invention may receive a patent unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102. *See Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302 (Fed. Cir. 1995) ("Invalidity based upon lack of novelty (often called 'anticipation') requires that the same invention . . . was known or used by others before it was invented by the patentee.") The application for the '265 patent was filed with the PTO on February 12, 1988, but claims priority from two French patent applications filed on February 17, 1987 and November 27, 1987, respectively. (Fact Stmt. at ¶ 9.) A patent is invalid due to anticipation when "each and every limitation is found either expressly or inherently in a single prior art reference." *See Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

In addition, the prior art reference must be "an enabling disclosure," rather than mere "vague intimations of general ideas that may or may not be workable." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (citing *Brenner v. Manson*, 383 U.S. 519, 536, 86 S. Ct. 1033, 16 L. Ed. 2d 69 (1966)). "Accordingly, invalidity by anticipation requires that the four corners of a single, prior art

reference describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). However, a disclosure is an "enabling disclosure" if a person of ordinary skill in the art "could have combined the publication's description of the invention with his own knowledge to make the claimed invention," *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006) (quoting *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985)), and the fact "[t]hat some experimentation is required to practice the claimed invention is permissible, so long as it is not undue." *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003).

2. *Discussion*

As a preliminary matter, the burden of showing invalidity is "especially difficult" when "the infringer attempts to rely on prior art that was before the patent examiner during prosecution." *See Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004) (citing *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999)). Here, not only was the prior art patent – the '596 patent – before the patent examiner during the prosecution of the '265 patent, but also the very same patent examiner, Bernard Dentz, approved both the '596 patent and the '265 patent.

a. *The '596 Patent Does Not Explicitly or Inherently Describe Clopidogrel Bisulfate*

Apotex relies on the '596 patent or its Canadian counterpart – the '875 patent – for its anticipation defense. The Court finds that Apotex has not proved by clear and convincing evidence that either patent describes clopidogrel bisulfate.

Claim 3 of the '265 patent, which claims clopidogrel bisulfate, reads as follows:

> Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thienopyridl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

'265 patent at col. 12. ll. 37-40. Thus, the claim consists of the following key limitations: (1) the bisulfate salt of (2) the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. (*See* Order dated May 7, 2004.)

Claim 2 of the '596 patent, in contrast, reads as follows:

> Methyl α-(4,5,6,7-tetrahydro-thieno(3,2,c)-5-pyridyl)-o.chlorophenyl-acetate.

'596 patent at col. 13, ll. 19-20. In the '596 patent specification, Claim 2 is exemplified as Example 1, which describes the hydrochloride salt of PCR 4099. '596 patent at col. 3, ll. 36-57.

In its decision affirming this Court's grant of a preliminary injunction in favor of Sanofi, the Federal Circuit found that "the plain language of claim 2 [of the '596 patent] only recites the free base,

MATTPCA, and does not expressly describe the dextrorotatory or levorotatory enantiomers or any salt. Because claim 2 [of the '596 patent] fails to describe each and every limitation of claim 3 [of the '265 patent] on its face, claim 2 does not anticipate claim 3." *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1376 (Fed. Cir. 2006), *reh'g denied*, 2007 U.S. App. LEXIS 2807 (Fed. Cir. Jan. 19, 2007). Nothing in the trial record changes the plain language of the patents, and this Court therefore reaches the same conclusion on a complete record as this Court and the Federal Circuit reached on a more limited record: Claim 2 of the '596 patent does not expressly describe clopidogrel or its bisulfate salt.[9] The Court also finds that Example 1 does not expressly describe clopidogrel bisulfate – there is no explicit reference to the enantiomers of PCR 4099 in that example and the particular salt described is the hydrocholoride, not the bisulfate.

The more difficult question is whether the additional limitations – namely the dextrorotatory enantiomer and its bisulfate salt – are inherently described elsewhere in the '596 patent. "Inherent

---

[9] That conclusion is supported by the absence from Claim 2 of the limitation which appears in Claim 1 – that the compounds within the genus "[include] both enantiomeric forms or their mixture." Because that language does not appear in Claim 2, it is appropriate to infer that Sanofi did not intend Claim 2 to cover the enantiomers of PCR 4099. *See Seachange Int'l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1368 (Fed. Cir. 2005) (quoting *Karlin Tech. Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999)) (applying "the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope").

anticipation requires that the 'missing characteristic is necessarily present, or inherent, in the single anticipating reference.'" *Glaxo Group*, 376 F.3d at 1348-49 (quoting *Schering Corp.*, 339 F.3d at 1377); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) (quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.").

Claim 1 of the '596 patent claims a general formula and specifies that the compounds covered by that formula include:

> their addition salts with pharmaceutically acceptable mineral or organic acids . . . including both enantiomeric forms or their mixture.

'596 patent at col. 13, ll. 8-19. The parties have stipulated that clopidogrel bisulfate is a compound within the genus of Claim 1 of the '596 patent. (Fact Stmt. at ¶ 32.)

Claim 8, which is also relevant, reads as follows:

> A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid or with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

'596 patent at col. 14, ll. 5-11.

Apotex contends that importing the limitations of Claims 1 and 8 into Claim 2 or Example 1 of the specification discloses clopidogrel bisulfate to a person of ordinary skill in the art. Indeed, Claims 1 and 8 do make express reference to the claim limitations which are absent from Claim 2 – namely, that the invention disclosed by the '596 patent includes the enantiomers of each racemic mixture and their formulation as pharmaceutically acceptable salts. Furthermore, some of the examples set forth in the specification – albeit not Example 1, which discloses PCR 4099 – are formulated as bisulfate salts.

Apotex's argument, however, is ultimately unpersuasive. First, it is undisputed that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004); *see also Atofina*, 441 F.3d at 999. In essence, patentability is not precluded by the fact that an inventor has identified or selected a single compound with particularly desirable qualities from a large class of previously patented compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 897 (S.D. Ind. 2005) ("Inventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements for patentability.") Although clopidogrel bisulfate concededly falls into the broad genus disclosed by Claims 1 and 8 – a genus which includes millions of possible compounds – a person of ordinary skill in the art would need to engage in impermissi-

ble "mechanistic dissection and recombination" of those disparate elements to arrive at the particular combination that is clopidogrel bisulfate. *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965); *see also Zenith Goldline*, 364 F. Supp. 2d at 900.

As noted above, Claim 2 describes the free base of PCR 4099 and Example 1 depicts PCR 4099 as a hydrochloride salt. However, neither of these disclosures describes the enantiomers of the racemate. *See Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 519 (D. Del. 2005), *aff'd in part, rev'd in part on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006) (noting that "courts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate"); *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978) ("[T]he novelty of an [enantiomer] is not negated by the prior art disclosure of its racemate.").

Despite the fact that the '596 patent covers millions of possible compounds when taking into account the full range of possible addition salts, Apotex invokes *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962), and *In re Schaumann*, 572 F.2d 312 (C.C.P.A. 1978) in support of the proposition that the '596 patent would be read by a person of ordinary skill in the art to describe a dramatically smaller genus of nine preferred compounds, including clopidogrel bisulfate.

In *Petering*, the Court of Customs and Patent Appeals upheld a Patent Board decision which had found that a claim covering several specific chemical compounds was anticipated by a prior art patent that had disclosed a class of compounds of which the spe-

cific compounds were members. 301 F.2d at 682. To reach that conclusion, the court identified "specific preferences" in the prior art patent that narrowed the generic formula to a limited subclass of approximately twenty compounds. *Id.* at 681. That same court reached a similar conclusion on similar facts in *Schaumann*, again noting the presence of a disclosed preference in the prior art patent. 572 F.2d at 316. *Petering* and *Schaumann* thus stand for the proposition that a genus may be small enough that its disclosure is equivalent to the description of each species within it. *See Petering*, 301 F.2d at 681-82; *Schaumann*, 572 F.2d at 316-17.

Apotex's proposed "sub-genus" consists of PCR 4099 and its levorotatory and dextrorotatory enantiomers, as well as three possible addition salts – the hydrobromide, the hydrochloride, and the bisulfate. This results in a subset of nine possible combinations out of the millions of combinations otherwise covered by the general formula disclosed in Claim 1 of the '596 patent. Apotex, however, has not persuaded the Court that the specification and claims of the '596 patent would have guided a person of ordinary skill to that particular subset.

First, Apotex contends that the pharmacological testing data in the '596 patent points a person of ordinary skill in the art directly to PCR 4099 and its enantiomers. That proposition, however, is undermined by several of this Court's findings. Most importantly, the testing data relied on by Apotex is based on screening tests that do not provide precise or sophisticated data. The tests did not, for example, involve a sufficient variety of doses of each compound from which ED_{50} values could be calculated. A person

of ordinary skill in the art would not use that data to rank the tested compounds against each other as a means of evaluating pharmacological activity, except where a particular compound showed virtually no platelet inhibition activity.

Furthermore, although PCR 4099 performed well in all four tests, other compounds also performed as well or, arguably, better, on one or more of the tests. Certainly, the results did not rule out the potential development of every other compound exemplified in the '596 patent apart from PCR 4099. The Court also notes that nothing in the '596 patent would have taught a person of ordinary skill in the art which of the tested compounds was the least toxic or best tolerated in animals or humans. The '596 patent specification describes all the compounds of the invention as exhibiting "an excellent tolerance and low toxicity." '596 patent at col. 8, ll. 41-49. That data, therefore, fails to support the proposition that the testing data disclosed in the '596 patent singles out PCR 4099 – and, by extension, its enantiomers – as the "specific preferences" of the inventors. Accordingly, the '596 patent would not direct a person of ordinary skill in the art to a "sub-genus" consisting of PCR 4099 and its enantiomers.[10]

---

[10] The fact that Sanofi publicized PCR 4099 at the San Diego and Jerusalem conferences in 1985 is inapposite for purposes of Apotex's contention that a person of ordinary skill in the art would have viewed PCR 4099 and its enantiomers as a subgenus. Anticipation requires that the claimed invention be described in a single, prior art reference; the disclosures of multiple references may not be combined. *See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 726-27 (Fed. Cir. 1984).

Second, Apotex contends that the examples in the '596 patent specification make clear that the three most likely salts forms would have been the hydrobromide, the hydrochloride, and the bisulfate. That contention is undermined by the fact that the person of ordinary skill in the art recognizes that there is no necessary correlation between the use of a particular pharmaceutically acceptable acid to form a crystalline salt with a racemate, on one hand, and the choice of acid to be used for the formation of a crystalline salt of the corresponding enantiomer, on the other. Thus, the fact that certain acids were used to purify the compounds exemplified in the '596 patent would not lead the person of ordinary skill in the art to a limited sub-genus involving only three salts. Although certain acids might – for a variety of reasons – be better candidates than others to use for the formulation of a pharmaceutical salt, the prior art would not have limited the choice of likely acids to only those three acids asserted by Apotex.

Accordingly, the full trial record compels the conclusion that the '596 patent does not direct a person of ordinary skill in the art exclusively to PCR 4099, its enantiomers, and three particular salt forms. In sum, the '596 patent does not inherently disclose clopidogrel bisulfate.

For largely the same reasons, the Canadian '875 patent does not describe clopidogrel bisulfate. The main distinction between the '875 patent and the '596 patent is that the former includes the language that "if desired," the enantiomers of any compound covered by the general formula may be isolated and prepared as a salt. This does nothing, however, to narrow the universe of possible compounds to the bi-

sulfate salt of the dextrorotatory enantiomer of a particular racemate – MATTPCA. Accordingly, the '875 patent also does not describe clopidogrel bisulfate.

b. *The '596 Patent Does Not Enable a Person of Ordinary Skill in the Art to Practice Clopidogrel Bisulfate Without Undue Experimentation*

Because the '596 patent does not expressly or inherently describe clopidogrel bisulfate, the Court need not determine whether the prior art patent enabled its practice. Nonetheless, even if one impermissibly engaged in "mechanistic dissection and recombination" of the various claims and examples of the '596 patent to piece together the elements of clopidogrel bisulfate, *see Ruschig*, 343 F.2d at 974, the Court finds that that patent did not enable a person of ordinary skill in the art "to practice the invention without undue experimentation." *Advanced Display Sys.*, 212 F.3d at 1282. *See Impax Labs.*, 468 F.3d at 1383 ("When a reference discloses a class of compounds, i.e., a genus, a person of ordinary skill in the art should be able to at once envisage *each member* of th[e] . . . class for the individual compounds, i.e. species, to be enabled.") (internal quotations omitted) (emphasis in original); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (finding that even if a presumption of enablement arises from the fact that a claimed compound falls within the genus of a prior art patent, the patentee can adduce evidence to prove that the disclosure is not enabling).

There is no serious dispute between the parties that a person of ordinary skill in the art for these purposes has a bachelor's degree in chemistry with a specialization in organic chemistry and would have several years experience in the field involved in the synthesis, study and properties of drugs, drug candidates, and biologically active compounds. This person would have both knowledge and experience in the preparation and separation of stereoisomers.

First, the '596 patent did not disclose to a skilled person how the enantiomers of PCR 4099 could be separated. Nothing in the prior art patent suggests, for example, that diastereomeric salt formation is the preferred means of obtaining the enantiomers of the racemic mixtures covered by the general formula of Claim 1. Although there were as many as ten different methods that a chemist might use to obtain the enantiomers of a racemate in 1987, the evidence proved that even if some of those methods could be immediately eliminated from consideration, there was no way to know which particular method or methods of the remaining options would be successful with a particular racemate. A chemist cannot be certain which method of separation or synthesis – or what configuration of variables presented by a particular method – will be effective for a given compound. Although the Canadian '875 patent states that "if desired" one can separate the enantiomers of the claimed compounds or make a salt, that statement does not demonstrate that undue experimentation would not be required to implement that suggestion. Discovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation.

even by one skilled in the relevant art. While not entirely dispositive, it is noteworthy that Sanofi – whose chemists were highly sophisticated and well-trained in the relevant art – spent a considerable amount of time trying to obtain the enantiomers of PCR 4099. If the '596 patent enabled clopidogrel, Sanofi would most certainly not have recorded numerous failed attempts using a variety of methods before attempting diastereomeric salt formation and obtaining the enantiomers.

Second, there is evidence, which is credited, that even if the enantiomers of a racemic mixture are obtained, a person of ordinary skill in the art must often experiment at length to formulate a suitable, crystalline salt when the prior art provides no guidance regarding what salt form of a particular compound will possess the required properties – the exact situation that confronted Sanofi in this case. As noted, the '596 patent provided no specific guidance that would have led a person of ordinary skill to prepare a methyl ester, or any enantiomer, as a bisulfate salt. Although the prior art – as a general matter – would have pointed a person of ordinary skill in the art to the universe of pharmaceutically acceptable acids, there are sufficient additional factors – including the risk that attempting to form a salt with certain acids will lead to racemization of the compound – such that the Court finds that preparing the free base of clopidogrel as a bisulfate salt also would have required a level of experimentation that was undue.

3. *Conclusion*

In view of the evidence and the applicable law, neither of the prior art patents – the '596 patent and its Canadian counterpart, the '875 patent – explicitly or inherently described the invention disclosed by Claim 3 of the patent-in-suit. Although the benefit of hindsight permits one to pull together the various claim limitations of clopidogrel bisulfate from the '596 patent or the '875 patent, these disparate references in each patent do not as a matter of law or fact anticipate the precise combination of elements described by Claim 3 of the '265 patent. Furthermore, neither the '596 patent nor the '875 patent provides specific guidance regarding how to obtain the enantiomers of any racemate covered by Claim 1, including PCR 4099, nor how to select a particular pharmaceutically acceptable acid to create a suitable salt form of a particular enantiomer. In sum, neither the '596 patent nor the Canadian '875 patent invoked by Apotex enable a person of ordinary skill in the art to practice the invention disclosed by the patent-in-suit without undue experimentation. Accordingly, Apotex has failed to show by clear and convincing evidence that clopidogrel bisulfate is anticipated by the '596 patent.

B. *Obviousness*

1. *Legal Standard*

A patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103. "Obviousness is a question of law which is predicated upon

several factual inquiries." *Ranbaxy Labs.*, 405 F. Supp. 2d at 516. To assess whether an invention is obvious, the Court considers: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence, or "secondary considerations," of nonobviousness, such as "commercial success, long felt but unsolved needs, [or] failure of others." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966). To this end, "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. Rather, a party alleging invalidity due to obviousness must articulate the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them." *Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1336 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006)).

Moreover, it is not enough for Apotex to have shown that the combination of claim limitations found in Claim 3 of the '265 patent would have been "obvious to try." *See In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out."); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990) ("[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103."). Rather, to establish obviousness, "a claimed *specific* compound" must be "precisely envisioned" by the prior art. *Deuel*, 51 F.3d at 1559 (emphasis in original). To

make that determination, the Court must assess, without the benefit of hindsight, whether the prior art would have suggested to a person of ordinary skill in the art that the invention should be made and that it would have a "reasonable likelihood of success." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

In addition, "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole.*" *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448 (Fed. Cir. 1984) (emphasis in original). Where the claimed invention is a chemical compound, the "compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). This principle requires the Court to determine whether clopidogrel bisulfate – including its properties – would have been obvious to a person of ordinary skill in the art as of February 17, 1987, the date on which the first French patent application for clopidogrel bisulfate was filed. Evidence that the compound exhibited unexpected or surprising properties rebuts a finding of prima facie obviousness. *In re Dillon*, 919 F.2d 688, 696 (Fed. Cir. 1990).

2. *Discussion*

According to Apotex, clopidogrel bisulfate was rendered obvious by the '596 patent because, after gaining familiarity with that patent, a person of ordinary skill in the art would have viewed as obvious the active enantiomer of PCR 4099 in the form of each of the three salts used for ester compounds in the examples of the '596 patent – namely, the hydro-

chloride, bisulfate and hydrobromide. Apotex also contends that a person of ordinary skill would have known that PCR 4099 held the most promise among the compounds disclosed by the '596 patent, a conclusion that would have been bolstered by Sanofi's own efforts to publicize PCR 4099 in the scientific community. A person of ordinary skill would also have known, in Apotex's view, that separating the enantiomers of PCR 4099 would elicit one active and one inactive enantiomer and that the enantiomer that exhibited antiplatelet activity would also be better tolerated. The person of ordinary skill in the art also would have viewed as obvious the preparation of that active enantiomer of PCR 4099 as each of the disclosed salt forms. Moreover, the '596 patent expressed the purpose behind the exercise – the search for a platelet aggregation inhibitor with a better activity/toxicity ratio than other drugs currently on the market. Thus, according to Apotex, the '596 patent also provided the motivation for a person of ordinary skill to synthesize clopidogrel bisulfate. Apotex further contends that regulatory trends in the mid-1980s favoring the development of enantiomers rather than their racemic mixtures – a trend that was forecasted by the prior art – provided additional motivation.

In sum, Apotex contends that the evidence demonstrates a prima facie case of obviousness. Indeed, in the case of chemical compounds where the prior art is "close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obvi-

ousness or a prima facie case of obviousness." *Dillon*, 919 F.2d at 696. "[E]ven though a patentee never must submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity – what we call a prima facie case – the patentee 'would be well advised to introduce evidence sufficient to rebut that of the challenger.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007) (quoting *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1570 (Fed. Cir. 1986)). Rebuttal evidence may consist of "a comparison of test data showing that the claimed composition[] possess[es] unexpectedly improved properties or properties that the prior art does not have." *Dillon*, 919 F.2d at 692-93. An "unexpected result" includes "some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Obviousness can also be rebutted by showing that "the prior art teaches away from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

The Court, therefore, must first consider whether Apotex has established a prima facie case of obviousness based on the prior art and, if so, whether Sanofi has effectively rebutted that presumption on the basis of the evidence submitted. For purposes of analysis, the Court assumes that Apotex has made a prima facie case of obviousness of the dextrorotatory enantiomer of PCR 4099 in view of the disclosure of the racemate in the '596 patent and the prior art teachings that (1) racemic compounds may be sepa-

rated into their enantiomers; and (2) those enantiomers, if obtained, may exhibit different biological activity or different degrees of the same type of biological activity exhibited by the racemate. Thus, the analysis will proceed directly to whether the specific properties exhibited by clopidogrel bisulfate-the invention, as a whole – would have been unexpected to a person of ordinary skill in the art.

Because a compound and its properties are one and the same, *see Papesch*, 315 F.2d at 391, evidence of the fact that any property of clopidogrel bisulfate is unexpected – as compared to PCR 4099 or anything else in the prior art – rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate. *See Ortho-McNeil Pharm., Inc. v. Myland Labs., Inc.*, 348 F. Supp. 2d 713, 760-61 (N.D. W. Va. 2004); *May*, 574 F.2d at 1092-93. In this regard, the Court concludes that the prior art did not enable a person of ordinary skill in the art to predict with a reasonable expectation of success whether one enantiomer of PCR 4099 would have better pharmaceutical properties than the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity. Moreover, the prior art would not have made obvious whether an isolated enantiomer of PCR 4099 would racemize in the body, serving to neutralize the gains achieved by separating the enantiomers.

Apotex contends that clopidogrel's lack of neurotoxicity should not be viewed as unexpected because Sanofi – prior to filing the application for the '265 patent – had not disclosed its internal testing

data which showed that PCR 4099 had a tendency to cause convulsions in animals. Moreover, Sanofi had publicized that PCR 4099 exhibited good tolerance and had even conducted human trials with the racemate. Apotex's argument, however, misapprehends the role of "unexpected properties" in the analysis of obviousness. To determine whether a given compound is obvious compared to a prior art compound, any and all properties of those compounds must be considered, even where the prior art has not disclosed the relevant properties of the prior art. *See Zenith Goldline*, 471 F.3d at 1378; *In re Lunsford*, 327 F.2d 526, 528 (C.C.P.A 1964).

Evidence of the course of Sanofi's research prior to securing the '265 patent also weighs in favor of the conclusion that separating the enantiomers of PCR 4099 would not have been obvious to a person of ordinary skill in the art at the relevant time. *See Dow Chem.*, 837 F.2d at 473; *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1544 (Fed. Cir. 1984). Sanofi spent four years and "tens of millions of dollars" developing and extensively testing the racemate PCR 4099 before deciding to try separating the enantiomers of the racemic mixture. (Maffrand PI Tr. 144.) The superiority of clopidogrel to PCR 4099 – which was only confirmed later – was clearly not obvious to the chemists at Sanofi. Apotex has not made a persuasive case to provide an explanation as to why the skilled chemists at Sanofi, furthermore, would have acted – as Apotex contends – so contrary to the hypothetical person of ordinary skill in the art.

Furthermore, the fact that the formulation of clopidogrel as a bisulfate salt results in a pharmaceutical compound possessing a highly favorable

combination of properties would also not have been obvious to a person of ordinary skill. There is undisputed testimony from experts for both sides that the bisulfate salt of clopidogrel has a highly favorable combination of properties: a high melting point, long-term stability, non-hygroscopic, and good solubility. Furthermore, the bisulfate salt was the *only* salt obtained by Sanofi that demonstrated that favorable combination of properties. That result was unexpected.

Apotex contends that a very recent decision of the Federal Circuit, *Pfizer, Inc. v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 2007 U.S. App. LEXIS 11886 (Fed. Cir. May 21, 2007), compels a different conclusion in this case. The Court, however, finds that *Pfizer* is distinguishable from this case. In *Pfizer*, the invention was the "besylate" salt of the antihypertensive drug amlodipine. 480 F.3d at 1352. Amlodipine had been specifically described in a prior Pfizer patent, and that prior art patent had described twelve illustrative pharmaceutically acceptable acid addition salts. *Id.* at 1353. The maleate was listed as the "preferred" salt and amlodipine was exemplified in that form in the prior art patent. *Id.* After obtaining that patent, however, Pfizer discovered that the maleate salt, for unforeseen reasons, was not suitable for the commercial manufacture of tablets due to stickiness and tablet degradation. *Id.* at 1353-54. The chemists at Pfizer attributed those problems to the particular chemical structure of the maleate salt – a reactive double bond in the maleate anion – which made the salt susceptible to degradation. *Id.* at 1362. Based on that knowledge, Pfizer chemists compiled a list of

seven salts, including besylate, which lacked the problematic double bond. *Id.* at 1354. After testing the various options, the besylate salt was found to be the most suitable alternative to the maleate. *Id.*

The Court finds, however, that *Pfizer* does not support the proposition that it would have been obvious to a person of ordinary skill in the art to formulate clopidogrel as a bisulfate salt. First, the chemists in *Pfizer* were able to identify the structural feature of the maleate salt that was causing problems, and, with that knowledge, were able to produce a short list of salts that they expected to solve the problem. In this case, importantly and by contrast to the situation in *Pfizer*, there were no structural features that would have guided Sanofi chemists in avoiding or selecting any specific acid.

Second, in *Pfizer*, the Federal Circuit noted that several prior art references, including patents, specifically suggested to a person of ordinary skill in the art that the use of the besylate salt would offer improved stability in the particular compound at issue. *Id.* at 1363. The Federal Circuit emphasized that the nature of the prior art in that case was such that the role of testing – after Pfizer chemists had identified the besylate salt as an option that they expected to succeed – was simply to verify the expected physicochemical characteristics of the salts identified. *Id.* at 1366-67. Here, there was no prior art teaching that the bisulfate salt was particularly likely to be a successful salt form of clopidogrel, and additional prior art – such as the Gould reference – might actually have led the person of ordinary skill in the art away from sulfuric acid, at least as an initial matter.

For these reasons and based on the findings of fact with respect to preparation of clopidogrel as a bisulfate salt, this Court concludes that *Pfizer* – which the Federal Circuit emphasized rested on its "particularized facts," *id.* at 1367 – does not control under the "particularized facts" of this case. Accordingly, the unexpected success of the bisulfate salt of clopidogrel – especially taking into account the lack of prior art directing a person of ordinary skill in the art to that particular outcome – independently supports the conclusion that Claim 3 of the '265 patent is non-obvious over the prior art.

As noted above, courts must also consider objective indicia, or "secondary considerations," of nonobviousness. *See Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667-68 (Fed. Cir. 2000). Whether an invention fulfills a "long-felt but unsolved" need, *see Graham*, 383 U.S. at 17-18, 35-36, was the only secondary consideration on which the parties offered extensive evidence in this case. At trial, the parties presented conflicting evidence regarding whether a long-felt need existed in the market for a more effective and safer platelet aggregation inhibitor and, more particularly, whether Plavix® filled that need. The Court need not resolve that debate. As this Court found following the preliminary injunction hearing, Sanofi's ownership of the '596 patent precluded anyone else from bringing clopidogrel bisulfate to market throughout the duration of that patent. For that reason, evidence relating to the "failure of others," a "long-felt but unsolved need," the "commercial success" of Plavix® – a factor on which the parties expressly did not present evidence at trial – and "copy-

ing" is undermined by the fact that those phenomena – to the extent they exist in this case – could have been derived from Sanofi's ownership of the '596 patent as much as from the nonobviousness of clopidogrel bisulfate. *See, e.g.*, *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (the inference drawn from a product's commercial success fails when others are legally barred from testing or practicing the invention given the existence of another patent covering that invention.) Although the Court has considered these secondary factors of nonobviousness – to the extent they were asserted by the parties at trial or find support in the record – the Court concludes that they do not relate to obviousness in this particular case.

3. *Conclusion*

This Court concludes that Sanofi has effectively rebutted a prima facie case of obviousness by demonstrating that clopidogrel bisulfate – as a whole – possesses unexpected properties that could not have reasonably been viewed as a likely outcome of preparing the invention. Whether or not it may have been "obvious to try" separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotary enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious. Sanofi's discovery that the bisulfate form of clopidogrel – a combination that the prior art did not predict would yield a Tier 3 salt with a highly desirable combination of properties – is an additional

basis for concluding the clopidogrel bisulfate was non-obvious on the relevant date.

C. *Double-Patenting*

The judicial doctrine of obviousness-type double-patenting prevents a patent claim from validly issuing when it "is obvious over, or anticipated by" a claim in an earlier patent. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). It is a "judge-made criterion adopted out of necessity where the courts were faced with a situation in which claims in two applications or patents were not drawn precisely to the *same* invention, but were drawn to inventions so very much alike as to render one obvious in view of the other and to effectively extend the life of the patent that would have [had] the earlier of the two issue dates." *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 686 (Fed. Cir. 1990) (emphasis in original).

The test for obviousness-type double-patenting is narrower than the statutory obviousness inquiry pursuant to 35 U.S.C. § 103. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003) ("Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application."); *Affymetrix, Inc. v. Pe Corp.*, 01 Civ. 0634, 2002 U.S. Dist. LEXIS 24649, at *5 n.3 (S.D.N.Y. Dec. 24, 2002) ("The same type of analysis is used for an obviousness-type double patenting inquiry as for a Section 103 obviousness inquiry, except that the scope of a double patenting inquiry is limited to only the claims

of the first patent, rather than the entirety of its disclosure.").

The double-patenting inquiry is subsumed by the broader statutory inquiry pursuant to 35 U.S.C. § 103 because Sanofi's entire '596 patent was prior art at the time the '265 patent issued. Because Apotex has failed to prove at trial that the '265 patent was obvious in light of the '596 patent as a whole, it has also necessarily failed to prove that the '265 patent was obvious in light of the specific claims of the '596 patent.

III. *Unenforceability Due to Inequitable Conduct Before the PTO*

Apotex contends that the '265 patent is unenforceable due to inequitable conduct by Sanofi when the patent was prosecuted before the PTO.

A. *Legal Standard*

"To hold a patent unenforceable for inequitable conduct, a court must find, by clear and convincing evidence, that the applicant omitted or misrepresented material facts with the intention of misleading of deceiving the patent examiner." *Monsanto Co. v. Bayer BioScience N.V.*, 363 F.3d 1235, 1239 (Fed. Cir. 2004). Both materiality and intent are questions of fact. *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1324 (Fed. Cir. 2000). Pursuant to 37 C.F.R. § 1.56, as in effect in 1988, certain individuals associated with the application for a patent have a duty of candor and good faith toward the PTO, which includes the duty to disclose to the PTO "information they are aware of which is material to the examination of the application." A breach of this duty

may constitute inequitable conduct rendering the patent unenforceable.

To demonstrate a failure to disclose material information, the party asserting inequitable conduct must show "(1) prior art that was material; (2) knowledge chargeable to an applicant of that prior art and of its materiality; and (3) failure of the applicant to disclose the art resulting from an intent to mislead the PTO." *Elk Corp.*, 168 F.3d at 30. Proof of inequitable conduct can be rebutted by "a showing that (a) the prior art was not material, (b) if the prior art was material, a showing that the applicant did not know of that art; (c) if the applicant did know of the art, a showing that the applicant did not know of its materiality; or (d) a showing that the applicant's failure to disclose the art did not result from an intent to mislead the PTO." *Id.* at 30.

"Information is 'material' when there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." *Id.* at 31. "[A]n otherwise material reference need not be disclosed if it is merely cumulative of or less material than other references already disclosed." *Id.*

With regard to intent to deceive the PTO, the Court must infer intent from the facts and circumstances surrounding Sanofi's overall conduct. *See Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1190 (Fed. Cir. 1993). However, the Court will not infer intent to deceive without clear and convincing evidence. *See Baxter Int'l Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1329 (Fed. Cir. 1998) ("[T]here must

be clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference."); *Old Town Canoe Co. v. Confluence Holdings Corp.*, 448 F.3d 1309, 1322 (Fed. Cir. 2006) (affirming district court's finding of no intent to deceive when party did "little more than urge this court to draw an inference of intent to deceive, arguing that the applicant or his attorney knew, or should have known that withheld information would be material").

B. *Discussion*

Apotex alleges that Sanofi made materially false statements and omitted material facts in an intentional effort to deceive the PTO examiner. Apotex first claims that Sanofi falsely represented to the PTO that the therapeutic activity of the dextrorotatory enantiomer was "unexpected." Second, Apotex asserts, Sanofi falsely informed the PTO examiner that the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers were surprising. Finally, Sanofi allegedly concealed that Dr. Maffrand was a true inventor of clopidogrel. Because, Apotex contends, Sanofi failed to name Dr. Maffrand as an inventor in the '265 patent, it was able to conceal both his knowledge that there was nothing unexpected about the properties of clopidogrel as well as the 1984 journal article co-authored by Dr. Robert Colman on this topic that Maffrand knew about and that allegedly should have been submitted as relevant prior art. Taking each of these allegations in turn, the Court concludes that Apotex has failed to prove by clear and convincing evidence that Sanofi engaged in inequitable conduct when prosecuting the '265 patent before the PTO.

1. *"Unexpected" Therapeutic Activity*

Apotex has not proven that Sanofi misled the examiner when it stated: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Ex. 9 at CLO-DRL 51362.)

As the Court concluded above, the properties of the dextrorotatory enantiomer of PCR 4099 were, taken together, unexpected in light of the prior art. Apotex contends that Sanofi's characterization of the therapeutic properties of clopidogrel as "unexpected" was false in light of Sanofi's prior work on thienopyridine compounds. The Court finds, however that, Sanofi's internal, non-public test data – particularly regarding PCR 1033 and its enantiomers – was not material. First, those results were non-public and not part of the prior art, and, therefore, could not effect the examiner's determination of whether clopidogrel bisulfate exhibited unexpected properties in light of the prior art. Even if that data had been disclosed, moreover, it did not provide any firm basis on which a person of ordinary skill in the art could reasonably have predicted the likely results of separating the enantiomers of PCR 4099 and preparing the active enantiomer as a bisulfate salt. If Sanofi had disclosed its conflicting data relating to both PCR 1033 and PCR 3549 – where the enantiomers of the former exhibited different levels of activity and the enantiomers of the latter exhibited equivalent activity – this would have confirmed that a skilled chemist would not have known *ex ante* whether PCR

4099's enantiomers would exhibit a significant split in therapeutic activity and toxicity.

Apotex also points to the written comments from Sanofi's French patent agent Jacqueline LaForest in 1987 as she helped to prepare the application for the French patent on clopidogrel bisulfate. Ms. LaForest replied to a draft of the French patent application with the handwritten remark, "[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner's hurdles without other results." (Def. Ex. 304.) Apotex alleges that this remark can only be taken as a reply to the draft phrase, "[i]n an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive." However, LaForest's comments were made in January 1987, before the results of March 1987 toxicology studies were known. These toxicology studies revealed what was – for purposes of review by the PTO – "unexpected" about clopidogrel, and that was the complete decoupling of therapeutic activity and neurotoxicity between the two enantiomers of the racemate. In addition, Laforest commented on the pharmacological activity yet also believed – mistakenly – that the relevant test results were not part of the application. As noted above, those very results in fact appeared in the draft application. Accordingly, the Court cannot credit Laforest's comment regarding a perceived lack of "surprising activity" in support of Apotex's allegations of inequitable conduct.

With respect to the memorandum from Michel de Haas dated December 30, 1986, the Court notes that these comments were made over a year after Dr. Maffrand first asked Badorc to pursue the isolation

of the enantiomers of PCR 4099 and nearly a month after Fréhel had already circulated his first draft of the French patent application for clopidogrel bisulfate – a draft in which the phrase "[i]n an unexpected manner" already appeared. Haas' speculation that the active enantiomer might offer a "major therapeutic advantage" was subsequently confirmed by the results of toxicology testing, which demonstrated that virtually all of the neurotoxicity associated with PCR 4099 was located in the inactive levorotatory enantiomer. Accordingly, the Court finds that the Haas memorandum fails to provide convincing evidence of any intent to mislead the PTO by inserting the phrase "[i]n an unexpected manner . . ." If anything, the Haas memorandum is simply a correct statement of the principle that the patentability of the dextrorotatory enantiomer depended on its unexpected properties – and the Court finds that those properties were, in fact, unexpected and discovered by Sanofi prior to the date that the U.S. patent application for clopidogrel bisulfate was filed.

2. *Tolerance*

Apotex's second allegation of inequitable conduct before the PTO concerns Sanofi's statement regarding the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers. Apotex asserts that Sanofi in fact had not conducted any tolerance testing at the time of the U.S. patent application, and thus had no data to support any assertions regarding how well clopidogrel was tolerated.

However, at the time of its '265 patent application, Sanofi had evidence from pharmacological and

toxicity studies that was relevant to how well clopidogrel was tolerated. Apotex primarily contends that the prior art recognizes a distinction between tolerance and toxicity. The record shows, however, that – at a minimum – the terms are closely related and are often used interchangeably, both at Sanofi and elsewhere. Furthermore, the Court finds that the patent examiner, Bernard Dentz, viewed the toxicity data included in the patent application as a sufficient basis for the statement that the levorotatory enantiomer was "less well tolerated" than clopidogrel. This strongly supports the Court's conclusion that the examiner was not misled by Sanofi's usage of the term "less well tolerated" in the patent application itself.

Apotex also relies on *Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1363-65 (Fed. Cir. 2003), and *Purdue Pharma L.P. v. Endo Pharmaceuticals Inc.*, 438 F.3d 1123, 1129-33 (Fed. Cir. 2006), to suggest that the accuracy of the statement depended exclusively on the existence of test data predating Fréhel's drafting of the original French patent application. But Apotex's reliance on those cases is misplaced. In those cases, unlike here, the patentees had made assertions about the properties of their inventions in the past tense – not the present – implying that they were relying exclusively on data obtained before the assertion was made. In this case, the data supporting the statement in the '265 patent application was presented in Table IV of the application, and Sanofi obtained additional data supporting the statement both before and after it applied for the U.S. patent.

In sum, there is no substantial evidence that any person with a duty of candor intended to mislead the examiner by describing the levorotatory enantiomer as less well-tolerated than clopidogrel. Indeed, there is no evidence that the examiner was misled.

3. *Dr. Maffrand's Knowledge*

Apotex's third inequitable conduct allegation is that Sanofi concealed that Dr. Maffrand was a true inventor of clopidogrel bisulfate, and that concealing his status facilitated Sanofi's concealment of his knowledge that there was nothing unexpected about the properties of clopidogrel, based on his prior work with PCR 1033. Withholding Dr. Maffrand's name, Apotex argues, enabled Sanofi to conceal a prior art journal article by Robert W. Colman and William R. Figures entitled "Characteristics of an ADP Receptor Mediating Platelet Activation" of which Maffrand was aware. Apotex contends that this article was "highly material" because it provided a basis for understanding the likely activity of various molecules – by describing characteristics of protein receptors relevant to platelet aggregation – which a reasonable PTO examiner would have found important.

As explained above, the Court finds that the Colman article was not material. Apotex has thus failed to prove that Sanofi had any reason to mislead the PTO as to the true inventorship of the claimed invention. There is no evidence that any person with a duty of candor to the PTO intended to mislead the PTO, either by failing to disclose the Colman article or by not including Dr. Maffrand as a named inventor on the patent application.

Accordingly, Apotex has failed to show by clear and convincing evidence that Sanofi engaged or intended to engage in any inequitable conduct in its prosecution of the '265 patent.

IV. *Equitable Considerations*

The Supreme Court has reiterated that there is no rule that a permanent injunction "automatically follows" a determination that a patent has been infringed. *See eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. ___, 126 S. Ct. 1837, 1840, 164 L. Ed. 2d 641 (2006). When a plaintiff seeks a permanent injunction in a patent case, a court must apply a traditional four factor test. Specifically, "[a] plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *Id.* at 1839. The decision to grant or deny permanent injunctive relief is "an act of equitable discretion" by the district court. *Id.*

In regard to the first two factors – irreparable injury and whether monetary damages are inadequate to make the patent holder whole – the Court concludes that both factors support the issuance of an injunction in this action. Sanofi has shown that it is likely to suffer irreparable price erosion, loss of goodwill, and a negative impact on the amount of research devoted to developing other medical uses for Plavix®. In regard to the third factor – i.e., whether "considering the balance of hardships between the

plaintiff and defendant, a remedy in equity is warranted" – the Court adheres to the analysis set forth upon issuing the preliminary injunction in this action, *see Sanofi-Synthelabo v. Apotex Inc.*, U.S. Dist. LEXIS 65127, at *75-78, and finds that the balance of hardships favors issuance of a permanent injunction. In regard to the fourth factor – i.e., "whether the public interest would not be disserved by a permanent injunction" – this involves essentially a balancing of the public interest in having access to generic drugs at reduced prices with the "significant public interest in encouraging the massive investment in research and development that is required before a new drug can be developed and brought to market." *Id.* at *80; *see Pfizer Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005). As in its analysis at the preliminary injunction phase of this action, the Court finds that the competing, important public interests in this litigation are either in equipoise or slightly favor Sanofi. In sum, utilizing the four part test set forth in eBay to guide the Court's discretion once it has concluded – as it has here – that a patent has been infringed and is valid and enforceable, this Court concludes that a permanent injunction is appropriate in this action.

V. *Conclusion*

Apotex has concededly infringed Sanofi's '265 patent. This Court now finds that Apotex has failed to prove by clear and convincing evidence that the '265 patent is invalid or unenforceable and Sanofi is entitled to a permanent injunction prohibiting Apotex from further infringement. 35 U.S.C. § 271(e)(4)(B). Damages will be set in an amount to

be determined through future proceedings. 35 U.S.C. §§ 271(e)(4)(C).

Accordingly, judgment will be entered in favor of Sanofi. Apotex, Inc. and Apotex Corp. and their agents, servants, employees, and other representatives, and all persons acting in concert with them, are hereby permanently enjoined from engaging in any activity that infringes U.S. Patent No. 4,847,265.

Dated: New York, New York
June 19, 2007

SO ORDERED:

/s/ Sidney H. Stein
Sidney H. Stein, U.S.D.J.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2007-1438

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., and
BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs-Appellees,

v.

APOTEX, INC. and APOTEX CORP.,

Defendants-Appellants.

[March 26, 2009]

Appeal from the United States District Court for the Southern District of New York in case no. 02-CV-2255, Judge Sidney H. Stein.

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellants,* and a response thereto having been

---

* Amicus Curiae, Golden Medical Supply, Inc. was granted leave to file a brief in support of the Appellants' combined petition for panel rehearing and rehearing en banc.

Apotex, Inc. and Apotex Corp. were granted leave to file a reply in support of their combined petition for panel rehearing and rehearing en banc.

invited by the court and filed by the Appellees, and the petition for rehearing and response, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for hearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on April 2, 2009.

FOR THE COURT,

/s/ Jan Horbaly
Jan Horbaly
Clerk

Dated: 03/26/09

FILED
U.S. COURT OF APPEALS
FOR THE FEDERAL CIRCUIT
MAR 26 2009
JAN HORBALY
CLERK

Supreme Court, U.S.
FILED
09-117 JUL 24 2009
OFFICE OF THE CLERK

134 (2)

No.

In the Supreme Court of the United States

APOTEX, INC. and APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

SUPPLEMENTAL APPENDIX

ROBERT B. BREISBLATT
Katten Muchin Rosenman LLP
525 W. Monroe Street
Chicago, IL 60661
(312) 902-5200

ROBERT S. SILVER
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street 11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of record
ALAN E. UNTEREINER
DANIEL R. WALFISH
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W. Suite 411
Washington, D.C. 20006
(202) 775-4500

SHASHANK UPADHYE
Apotex, Inc.
150 Signet Drive
Toronto, ON M9L 1T9
Canada
(416) 401-7701

TABLE OF CONTENTS

Pursuant to Supreme Court Rule 33(1)(c), petitioners have separately duplicated certain patent documents on 8½- by 11-inch paper in this Supplemental Appendix.

U.S. Patent No. 4,529,596 ..... S1

Canadian Patent No. 1,194,875 ..... S9

U.S. Patent No. 4,847,265 ..... S29

United States Patent [19]

Aubert et al.

[11] Patent Number: 4,529,596

[45] Date of Patent: Jul. 16, 1985

[54] THIENO [3,2-c] PYRIDINE DERIVATIVES AND THEIR THERAPEUTIC APPLICATION

[75] Inventors: Daniel Aubert, Plaisance Du Touch; Claude Ferrand, Ramonville Saint-Agne; Jean-Pierre Maffrand, Garonne, all of France

[73] Assignee: Sanofi, S.A., Toulouse, France

[21] Appl. No.: 510,582

[22] Filed: Jul. 5, 1983

[30] Foreign Application Priority Data

Jul. 13, 1982 [FR] France 82 12599

[51] Int. Cl.³ A61K 31/435; C07D 495/04

[52] U.S. Cl. 514/231; 514/301; 544/127; 544/362; 546/114

[58] Field of Search 546/114; 544/362, 127; 424/248.51, 250, 256

[56] References Cited

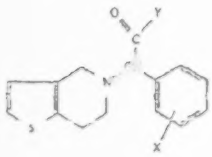
U.S. PATENT DOCUMENTS

2,527,574 10/1950 Ruevschi, Jr. 546/138

Primary Examiner—Henry R. Jiles
Assistant Examiner—Bernard L. Dentz
Attorney, Agent, or Firm—Weiser & Stapler

[57] ABSTRACT

This invention relates to new thieno [3,2-c] pyridine derivatives having the formula:



(I)

in which:

Y represents the OH group or an OR group in which R is a straight or branched lower alkyl radical, or Y represents a group

in which R_1 and R_2 are each independently of each other, hydrogen or a straight or branched lower alkyl group, or R_1 and R_2 form together and with the nitrogen atom to which they are attached a heterocycle which may include a second heteroatom such as oxygen or nitrogen, wherein the latter may be substituted by a lower alkyl or benzyl radical which may be substituted, and X represents hydrogen, a halogen or a lower alkyl radical; and their addition salts with pharmaceutically acceptable mineral or organic acids if Y represents the group OR or

or with mineral bases if Y represents OH, as well as the two enantiomers or their mixture.

The invention also relates to the preparation process of new thieno [3,2-c] pyridine derivatives and to their therapeutic application as blood-platelet aggregation inhibiting agents and antithrombotics.

12 Claims, No Drawings

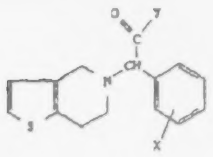
DEPOSITION EXHIBIT Pefts 1 3/26/03 TS

CLO-DRL 51129

S1

THIENO [3,2-c] PYRIDINE DERIVATIVES AND THEIR THERAPEUTIC APPLICATION

This invention relates to new thieno[3,2-c]pyridines, to a process for their preparation and to their therapeutic applications. The new derivatives of this invention have the following general formula:



(I)

in which:

Y represents the OH group or an OR group in which R is a straight or branched lower alkyl radical, or Y represents a group

in which R_1 and R_2 are each independently of each other hydrogen or a straight or branched lower alkyl group, or R_1 and R_2 form together and with the nitrogen to which they are attached a heterocycle which may include a second heteroatom such as oxygen or nitrogen, wherein the latter may be substituted by a lower alkyl or benzyl radical which may be substituted, and X represents hydrogen, a halogen or a lower alkyl radical.

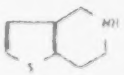
These compounds having an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture.

The invention also includes addition salts with pharmaceutically acceptable mineral or organic acids if Y represents the groups OR or

or with mineral bases if Y represents OH.

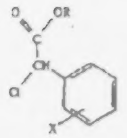
A lower alkyl radical is understood to mean a C_1–C_6 saturated hydrocarbon chain.

The invention also relates to a process for the preparation of compounds of the formula (I) as defined above, wherein the esters of the invention in which Y represents an OR group as defined above are prepared by condensation of 4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine, having the following formula:



(II)

with an α-chlorophenyl acetate having the following formula:



(III)

in which R and X have the above-defined meanings. Acids of formula (I), in which Y represents OH, are obtained by saponification.

To prepare the amides, in which Y represents a group

in which R_1 and R_2 have the above-defined meanings or even some esters of formula (I), the acid of formula (I)(R=OH) is reacted, after activation if required, either with the amine

or with the alcohol R—OH.

The α-halogenated esters of the formula (III) are prepared using known methods (E. L. ELIEL, M. T. FISK and T. PROSSER, Organic Syntheses, Coll. Vol. IV, J. WILEY and SONS, Inc. New York, 1963, p. 169).

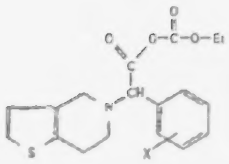
Although it is possible to obtain all the esters of formula (I) by the reaction between the compounds of formulae (II) and (III), for economic reasons it is preferable to prepare certain higher esters of the formula (I) from the acid of formula (I) and alcohol (R—OH).

The condensation of the tetrahydro-thieno-pyridine with the ester of formula (III) is effected in the presence of an alkali metal carbonate, such as potassium carbonate for example, in an inert solvent such as dimethylformamide, tetrahydrofuran or 1,2-dimethoxy ethane, at temperatures between 60° C. and the boiling point of the solvent.

The saponification of the ester of formula (I) in which R is methyl or ethyl is effected by an alkali metal hydroxide such as sodium or potassium hydroxide in a hydroalcoholic solvent, at temperatures between room temperature and the boiling point of the solvent.

Activation of the acid of formula (I) may be obtained by treatment with ethyl chloroformate in the presence of a slight excess of triethylamine at temperatures between −5° C. and 0° C. in an inert solvent such as chloroform, 1,2-dimethoxy ethane or tetrahydrofuran.

A mixed anhydride having the following formula



(IV)

is formed and if treated in situ with a slight excess either of alcohol or amine, at temperatures between 10° C. and room temperature, the esters or amides of the formula (I) will be formed respectively.

The activation of the acid of formula (I) may also be obtained in different ways: the amides of formula (I) were also thus prepared by condensing the acid (I) with the amine

in the presence of dicyclohexylcarbodiimide in solution in 1,2-dichloro-ethane.

The esters of formula (I) may also be obtained in the conventional manner by condensing the corresponding acid and alcohol (ROH) in the presence of hydrochloric gas or thionyl chloride.

The following non-limiting Examples are given to illustrate the invention.

EXAMPLE 1

Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate (R_1 = —CH_3; X = 2-Cl) derivative No. 1.

3.47 g (0.144 mole) of methyl 2-chloro-α.chlorophenylacetate and 19.82 g (0.144 mole) of potassium carbonate are added to a 20 g (0.144 mole) solution of 4,5,6,7-tetrahydro thieno[3,2-c]pyridine in 200 ml of dimethylformamide. The solution is then heated for four hours at 90° C. The reaction mixture is cooled to room temperature, the mineral salts are filtered and the solvent is evaporated. The residue is taken up in water and then extracted with ethylic ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated, to give a yellow oil which is purified by means of its hydrochloride. White crystals. M.p. = 130°-140° C. (ethylacetate, isopropanol). Yield: 45%.

EXAMPLE 2

Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]phenylacetate (R_1 = —CH_3; X = H) derivative No. 2.

This compound is prepared by the same procedure described in Example 1 by alkylation of the 4,5,6,7-tetrahydro thieno[3,2-c]pyridine with methyl 2-chlorophenylacetate. Hydrochloride; white crystals softening point = 200° C. (ethanol). Yield: 70%.

EXAMPLE 3

Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-α.fluorophenylacetate (R_1 = —CH_3; X = 2-F) derivative No. 3.

This compound is prepared by the same procedure as described in Example 1 by alkylation of 4,5,6,7-tetrahydro thieno[3,2-c]pyridine with methyl 2-chloro-α.fluoro-phenylacetate. Hydrochloride; white crystals; M.p. = 100° C. Yield: 76.5%.

EXAMPLE 4

Ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-α.methyl-phenylacetate. (R_1 = —CH_2—CH_3; X = 2-CH_3) derivative No. 4.

This compound is prepared by the procedure described in Example 1 by alkylation of 4,5,6,7-tetrahydro thieno[3,2-c]pyridine with ethyl 2-chloro-α.methyl-phenylacetate. Bisulphate; white crystals: M.p. = 188°-190° C. (isopropanol). Yield: 54%.

EXAMPLE 5

α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-α.chlorophenylacetic acid. (R_1 = H; X = 2-Cl) derivative No. 5.

A mixture of 157.9 g of ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-α.chloro-phenylacetate and 100 ml of a 30% sodium hydroxide solution in 600 ml of ethanol is heated under reflux for 2 hours 30 minutes. After evaporation of the ethanol, the mixture is acidified with glacial acetic acid and extracted with methylene chloride. The organic phase is washed with water, dried over magnesium sulphate and then evaporated. After recrystallization in water, the product is isolated in monohydrate form. White crystals; Softening point = 125° C. (water). Yield: 46%.

EXAMPLE 6

α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetic acid. (R_1 = H; X = H) derivative No. 6.

This compound is prepared by the procedure described in Example 9 by saponification of ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetate. The product is purified by means of its sodium salt.

White crystals: M.p. = 210°-215° C. (ethanol, mechanol).

Yield: 74%.

EXAMPLE 7

n-Propyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-α.chloro phenylacetate. (R_1 = —CH_2—CH_2—CH_3; X-2-Cl) derivative No. 7

A stream of hydrochloric gas is bubbled through a 10 g (0.0306 mole) solution of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-α.chlorophenylacetic acid monohydrate (Example 5) for 12 hours in 100 ml of n-propanol which is refluxed. The mixture is evaporated and the residue is taken up in water, basified with sodium bicarbonate and extracted with ethylic ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated to give a yellow oil which is purified by means of its bisulphate. White crystals. M.p. = 146° C. (crude). Yield: 78%.

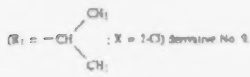
EXAMPLE 8

n-Butyl
α-[4,5,6,7-tetrahydro-thieno[3,2-c] 5-pyridyl]-o.chloro-phenylacetate. (R_1 = —CH_2—CH_2—CH_2—CH_3; X = 2-Cl) derivative No. 8.

This compound is prepared by the procedure described in Example 5 by esterification of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.-chloro-phenylacetic acid monohydrate (Example 5) with n-butanol. Purified using the bisulphate; white crystals; M p = 155° C. Yield: 79.5%.

EXAMPLE 9

Isopropyl
α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.-chloro-phenylacetate.



(R_1 = —CH(CH$_3$)(CH$_3$); X = 2-Cl) derivative No. 9.

2 ml of thionyl chloride are added dropwise to a 1 g (0.0031 mole) suspension of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chloro-phenylacetic acid monohydrate (Example 5) in 20 ml of isopropanol cooled to −10° C. The reaction mixture is then refluxed for 6 hours. After evaporation, the residue is taken up in water, basified with sodium bicarbonate and extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulphate and evaporated. A colourless resin is collected and purified using the bisulphate.

White crystals: softening point = 140°-150° C.
Yield: 44%.

EXAMPLE 10

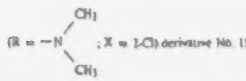
Ethyl
α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chloro-phenylacetate. (R_1 = CH_2—CH_3, X = 2-Cl) derivative No. 10.

4.86 ml (0.051 mole) of ethylchloroformate are added dropwise to a 15 g (0.046 mole) solution of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.phenylacetic acid monohydrate (Example 5) and 7.12 ml (0.051 mole) of triethylamine in 150 ml of chloroform, cooled to a temperature between −5° and 0° C. The mixture is then allowed to return to room temperature and is stirred for 30 minutes. The reaction mixture is then cooled to a temperature of around 10° C. and 30 ml of ethanol are added dropwise. The reaction mixture is stirred at room temperature for one night and is then washed with water. The organic phase, dried over sodium sulphate, is evaporated to give a colourless oil which is purified by means of its hydrobromide.

White crystals: M p. = 180° C.
Yield: 94%.

EXAMPLE 11

N,N-dimethyl
α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chloro-phenylacetamide.



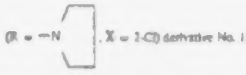
(R = —N(CH$_3$)(CH$_3$); X = 2-Cl) derivative No. 11.

9.72 ml (0.102 mole) of ethyl chloroformate are added dropwise to a 30 g (0.092 mole) solution of α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chloro-phenylacetic acid monohydrate and 14.24 ml (0.102 mole) of triethylamine in 300 ml of chloroform, cooled to a temperature between −5° and 0° C. The mixture is then allowed to return to room temperature and is stirred for 30 minutes. The reaction mixture is then cooled to a temperature of around 10° C. and 4.57 ml (0.102 mole) of dimethylamine are added dropwise to 60 ml of chloroform and the mixture is stirred at room temperature for one night. Water is added, the mixture is decanted, and the organic phase is dried over sodium sulphate and evaporated. A colourless resin is collected, which then crystallizes.

White crystals: M.p. = 95°-100° C. (isopropylic ether).
Yield: 49%.

EXAMPLE 12

1-[(2-chloro phenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl-)acetyl]-pyrrolidine.



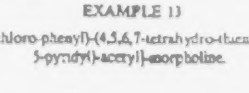
(R = —N(CH$_2$)$_4$; X = 2-Cl) derivative No. 12.

This compound is prepared by the procedure described in Example 11 by condensing α-(4,5,6,7-tetrahydro-thieno(2,3-c)-5-pyridyl]-o.chloro-phenylacetic acid monohydrate with pyrrolidine.

White crystals: M p. = 130° C. (isopropylic ether).
Yield: 61.5%.

EXAMPLE 13

1-[(2-chloro-phenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-acetyl]-morpholine.



(R = —N(CH$_2$)$_2$O(CH$_2$)$_2$; X = 2-Cl) derivative No. 13.

2.67 g (0.031 mole) of morpholine are added to a 10 g (0.031 mole) solution of α-[4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl]-o.chloro-phenylacetic acid monohydrate and 13.3 g (0.064 mole) of dicyclohexyl carbodiamide in 100 ml of 1,2-dichloro ethane and the mixture is stirred at room temperature for one night. The mixture is evaporated then taken up with 2N hydrochloric acid and ethylic ether. After filtering the dicyclohexylurea formed, the filtrate is decanted and the aqueous phase is basified with 2N sodium hydroxide then extracted with methylene chloride. The organic

phase is washed with water, dried over sodium sulphate and evaporated to give a yellow resin which is purified by means of its hydrochloride hemihydrate.

White crystals: M.p. = 215°-255° C. (isopropanol).

Yield: 71%

EXAMPLE 14

1-[(2-chloro phenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-acetyl]-piperidine.

(R = —N ; X = 2-Cl) derivative No. 14

This compound is prepared by the procedure described in Example 13 by condensing α-[4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl]-o.chloro-phenylacetic acid monohydrate with piperidine.

White crystals: M.p. = 139° C. (isopropanol).

Yield: 51.5%.

The following compounds were prepared by the process described in Example 11:

[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl]-o.chlorophenylacetamide. (R = —NH_2; X = 2-Cl). derivative No. 15.

White crystals; M.p. = 126°-128° C. (isopropylic ether-isopropanol).

Yield: 46%.

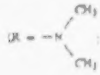
4-benzyl-1-[(2-chloro-phenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)acetyl] piperazine

(R = —N —CH_2— ; X = 2-Cl) derivative No. 16

oxalate: white crystals. M.p. = 178° C. (ethanol).

Yield: 82.5%.

N,N-dimethyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.fluoro-phenylacetamide.



(R = —N ; X = 2-F) derivative No. 17

Slightly yellowish powder; M.p. = 125° C. (isopropylic ether-isopropanol).

Yield: 61%.

N-methyl-[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o chloro-phenylacetamide. (R = NH—CH_3 X = 2-Cl)—derivative No. 18.

White crystals: M.p. = 137° C. (isopropanol).

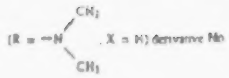
Yield: 85.5%.

N-benzyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chloro-phenylacetamide. (R = —NH—(CH_2)—CH_3; X = 2-Cl)—derivative No. 19

White crystals: M.p. = 102° C. (isopropylic ether).

Yield: 55%

N,N-dimethyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)phenylacetamide.

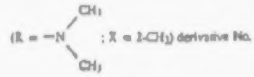


(R = —N ; X = H) derivative No. 20

White crystals: M.p. = 138° C. (isopropylic ether).

Yield: 39%.

N,N-dimethyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o methyl-phenylacetamide.



(R = —N ; X = 2-CH_3) derivative No. 21.

White crystals: M.p. = 119° C. (hexane).

Yield: 15%

The results of pharmacological and toxicological tests reported below demonstrate the properties of the derivatives of the invention both in terms of toxicity and tolerance, and the activity levels of the derivatives, especially their inhibiting action on blood-platelet aggregation and anti-thrombotic activity.

Thus, the invention also relates to a therapeutic composition having in particular an inhibiting action on blood-platelet aggregation and anti-thrombotic action, wherein the active ingredient is a derivative of the formula (I) or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid if Y represents the groups OR or

and with a mineral base if Y is OH.

TOXICOLOGICAL INVESTIGATION

The compounds of the invention exhibit an excellent tolerance and a low toxicity.

In addition, the tests carried out on acute, chronic, sub-chronic and delayed toxicity in various animal species showed no local or general reaction, no disturbances or abnormalities in the biochemical, macroscopic and microscopic examinations performed during this experiment.

PHARMACOLOGICAL INVESTIGATION

(1) Inhibiting action on blood-platelet aggregation

This experiment was performed on rats. The compound to be tested was administered orally in the form of a suspension in gum arabic to the rats over a 3-day period 48 hours, 24 hours and 2 hours before taking a 4 ml blood sample from the animals using Renaud's method from their jugular veins under anaesthetic. The citrated blood was used in the aggregation determinations.

(a) Determination of A.D.P.-induced blood-platelet aggregation.

2 ml of citrated blood were poured quickly into a small beaker placed in a magnetic stirrer, fitted with a magnetic bar. After a few seconds of agitation, 0.4 ml of a solution containing 0.66 mg of adenosine-diphosphate (A.D.P.) per ml was placed in the beaker. After 30 sec-

CLO-DRL 51133

S5

onds of stirring, two 0.5 ml samples of blood were taken:

the first was mixed with 0.5 ml of an EDTA-formol solution

the second was mixed with 0.5 ml of a solution of EDTA only

The purpose of adding EDTA formol is to stabilize the blood and thus to fix the aggregation whereas EDTA alone causes disaggregation of all the platelet clusters.

After leaving the mixtures at rest for 10 minutes and centrifuging the two mixtures at low speed for 5 minutes in order to separate the red corpuscles, the supernatant platelet-rich plasma (PRP) was removed, diluted and a platelet count was made.

The intensity of the aggregation was determined by the following ratio:

$$\frac{\text{number of platelets in EDTA-formol}}{\text{number of platelets in EDTA}} \times 100 = \text{percentage of non-aggregated platelets.}$$

The blood-platelet aggregation inhibiting action of the product tested improves as the ratio approaches 100.

The results showing the mean percentage of non-aggregated platelets in groups of 5 rats (treated and reference groups) are shown in Table I

TABLE I

	ADP TEST		
PRODUCT	DOSAGE mg/kg	ROUTE*	RESULT
Reference group	3 x 25	P.O.	16 ± 4
Derivative No. 1		—	94 ± 3
Reference group	3 x 5	—	20 ± 11
Derivative No. 1		—	82 ± 11
Reference group	3 x 2.5	—	23 ± 15
Derivative No. 1		—	36 ± 17
Reference group		—	8 ± 0
Derivative No. 10	3 x 25	—	66 ± 2
Derivative No. 10	3 x 12.5	—	49 ± 11
Reference group	3 x 10	—	8 ± 1
Derivative No. 10		—	24 ± 5
Reference group	3 x 60	—	11 ± 0
Derivative No. 9		—	65 ± 7
Reference group	3 x 100	—	83 ± 3
Derivative No. 4		—	89 ± 1
Reference group	3 x 100	—	3 ± 1
Derivative No. 4		—	89 ± 4
Reference group	3 x 100	—	4 ± 0
Derivative No. 2		—	71 ± 12
Reference group	3 x 100	—	4 ± 0
Derivative No. 12			27 ± 5
Reference group		—	3 ± 0
Derivative No. 17	3 x 100	—	91 ± 3
Derivative No. 20	3 x 100	—	4 ± 1
Reference group	3 x 100	—	18 ± 1
Derivative No. 6		—	22 ± 4

*Route of administration

(b) Determination of collagen induced blood platelet aggregation

0.10 ml of a solution containing 1.0 ug of collagen per ml was added to 1.5 ml of citrated blood. With the mixture being agitated, the platelets were counted continually.

The reduction of the number of free platelets over time was continuously measured and a curve was plotted showing the actual aggregation rate.

The results, representing mean values determined on each group of 5 rats (treated and reference groups), are shown in Table II

TABLE II

	COLLAGEN TEST		
PRODUCT	DOSAGE mg/kg	ROUTE*	RESULT
Reference group	3 x 25	P.O.	3.12 ± 0.41
Derivative No. 1		—	0.14 ± 0.03
Reference group	3 x 5	—	3.17 ± 0.84
Derivative No. 1		—	0.19 ± 0.09
Reference group	3 x 2.5	—	3.60 ± 1.02
Derivative No. 1		—	0.40 ± 0.20
Reference group		—	3.92 ± 0.63
Derivative No. 10	3 x 25	—	0.16 ± 0.07
Derivative No. 10	3 x 12.5	—	0.54 ± 0.12
Reference group		—	3.00 ± 0.35
Derivative No. 9	3 x 100	—	0.46 ± 0.18
Derivative No. 4	3 x 100	—	0.88 ± 0.18
Reference group	3 x 60	—	3.23 ± 0.33
Derivative No. 9		—	0.11 ± 0.01
Reference group	3 x 100	—	3.41 ± 0.55
Derivative No. 4		—	0.17 ± 0.03
Reference group	3 x 100	—	4.73 ± 0.55
Derivative No. 4		—	0.30 ± 0.02
Reference group	3 x 100	—	3.00 ± 1.06
Derivative No. 2		—	0.31 ± 0.18
Reference group	3 x 100	—	3.25 ± 0.12
Derivative No. 12		—	0.83 ± 0.02
Reference group	3 x 100	—	2.77 ± 0.12
Derivative No. 14		—	1.89 ± 0.13
Reference group	3 x 100	—	3.99 ± 0.40
Derivative No. 19		—	2.32 ± 0.68
Reference group	3 x 100	—	3.01 ± 0.79
Derivative No. 21		—	1.04 ± 0.12
Reference group	3 x 100	—	11.35 ± 1.01
Derivative No. 18		—	10.82 ± 0.8

*Route of administration

(c) Determination of bleeding time

The study of the blood-platelet aggregation inhibiting action also concerned the action of the compound of the invention on bleeding time.

The method used is an adaptation of the method of L. STELLA, M. B. DONATI and G. de GAETANO, Thromb. Res., 1975, 7, 709–716.

The experiment was performed on rats. The compound to be tested was administered to the animals per os in suspension in 10 ml/kg of a 5% aqueous solution of gum arabic 65 hours, 41 hours and 17 hours prior to determination. After anesthetizing the animals with pentobarbital, their tails were cut 5 mm from the ends. The blood was carefully sponged at 15-second intervals taking care not to touch the wound.

Hemostasis was reached when the bleeding stopped for one minute.

The results representing mean bleeding times in seconds, determined in each group of 5 rats (reference and treated groups), are given in Table III. Times longer than 1200 seconds (20 minutes) were not counted.

TABLE III

	BLEEDING TIME		
PRODUCT	DOSAGE mg/kg	ROUTE*	RESULT
Reference group		P.O.	600
Derivative No. 10	3 x 100	—	1 200
Derivative No. 2	3 x 100	—	1 200
Reference group		—	420
Derivative No. 1	3 x 25	—	1 200
Derivative No. 1	3 x 5	—	1 020
Reference group	3 x 12.5	—	420
Derivative No. 1		—	1 200
Reference group	3 x 100	—	780
Derivative No. 1		—	1 200
Reference group	3 x 100	—	660
Derivative No. 18		—	1 200
Reference group	3 x 100	—	900

CLO-DRL 51134

TABLE III-continued

PRODUCT	BLEEDING TIME DOSAGE mg/kg	ROUTE*	RESULT
Derivative No. 12		—	1 200

*Route of administration

(2) Anti thrombotic activity

This activity was studied by the silk thread experimental thrombosis method.

The principle of this study is an adaptation of the experimental thrombosis method using cardiopulmonary by-pass described by TERUHIKO UMETSU and KAZUKO SANAI (THROMB. HAEMOST., 39. 1. 1978).

The animals' left jugular veins and right external carotid arteries were uncovered (the rats were anesthetized by intraperitoneal injection of pentoburbital.

The arteriovenous shunt consists of a central catheter and two lateral catheters; a white raw silk thread is inserted in the central part and circulation is restored for 20 minutes. After stopping circulation by clamping, the thread is gently withdrawn and weighed immediately. As the average weight of a wet silk thread was previously determined, the weight of the thrombus is determined by evaluation the difference.

The treatment is applied 48 hours, 24 hours and 2 hours before the start of blood flow in the shunt by oral administration of the compound to be tested in suspension in 10 ml/kg of 5% gum arabic, while only the 5% gum arabic solution is administered to the reference group.

The results showing the weight of the thrombus in mg are given in Table IV.

TABLE IV

PRODUCT	DOSAGE mg/kg	ROUTE*	ANTI THROMBOTIC ACTIVITY WEIGHT OF THROMBOSIS IN mg	PERCENTAGE VARIATION
Reference group	3 × 200	P.O.	38.56 ± 3.42	−22
Derivative No. 8		—	29.99 ± 3.05	
Reference group	3 × 200	—	42.65 ± 3.30	−94
Derivative No. 3		—	2.60 ± 0.24	
Reference group		—	36.24 ± 2.05	
Derivative No. 9	3 × 25	—	0.36 ± 0.33	−82
Derivative No. 5	3 × 12.5	—	15.98 ± 1.81	−36
Reference group	3 × 5	—	40.86 ± 2.03	−22
Derivative No. 1		—	27.7 ± 2.82	
Reference group		—	40.68 ± 1.74	
Derivative No. 2	3 × 200	—	8.43 ± 3.28	−79
Derivative No. 10	3 × 200	—	5.89 ± 0.99	−84
Reference group	3 × 200	—	33.76 ± 1.76	−40
Derivative No. 11		—	24.28 ± 4.92	

*Route of administration

The toxicological and pharmacological investigations reported above demonstrate the low toxicity of the compounds of the invention, as well as their excellent tolerance and their inhibiting properties on blood-platelet aggregation, and their anti-thrombotic activity, which make them very useful in medical therapeutic applications.

The drug of the invention may be orally administered in the form of tablets, coated tablets, capsules, drops, granules or syrup. The drug can also be provided in the form of suppositories for rectal administration or in the form of solution for injection for parenteral administration.

Each unit dose contains advantageously from 0.005 g to 0.250 g of a derivative of the invention, the daily dosage regimen varying within a range from 0.005 g to 1.00 g active ingredient according to the age of the patient and the severity of the disease to be treated.

Non-limiting examples of pharmaceutical formulations of the medicine of this invention are given below.

(1) Tablets

Derivative No. 1 . . . 0.050 g

Excipient: lactose, icing sugar, rice starch, alginic acid, magnesium stearate.

(2) Coated tablets

Derivative No. 10 . . . 0.100 g

Excipient: magnesium stearate, corn starch, gum arabic, shellac, white sugar, glucose, white wax, carnauba wax, paraffin, new cochinealin.

(3) Capsules

Derivative No. 17 . . . 0.100 g

Excipient: magnesium stearate, corn starch, lactose

(4) Solution for injection

Derivative No. 4 . . . 0.075 g

isotonic solvent sufficient to make 3 ml

(5) Suppositories

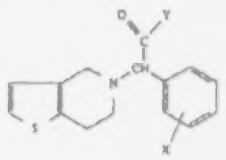
Derivative No. 21 . . . 0.100 g

Semi-synthetic triglycerides sufficient to make 1 suppository.

We claim:

1. A compound of the formula:

(I)



in which Y represents hydroxyl, an OR group wherein R is a straight or branched lower alkyl radical, or

in which R_1 and R_2 are each independent of each other and represent hydrogen or a straight or branched lower alkyl group; or R_1 and R_2 form together with the nitrogen atom to which they are attached a heterocycle selected from the group consisting of pyrrolidino, piperidino, morpholino, piperazino, N-lower alkyl piperazino and N-benzyl piperazino; and X represents hydrogen, a halogen or a lower alkyl radical; and their addition salts with pharmaceutically acceptable mineral or organic acids if Y represents OR groups or

or with mineral bases if Y represents OH, including both enantiomeric forms or their mixture.

2. Methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chlorophenyl-acetate.

3. Methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)phenylacetate.

4. Methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o fluoro-phenylacetate.

5. Isopropyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chloro-phenylacetate.

6. Ethyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chloro-phenylacetate.

7. N,N-dimethyl-[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o.chlorophenylacetamide.

8. A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid or with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

9. The composition as claimed in claim 8, in unit dosage form.

10. The composition as claimed in claim 8 or 9 in unit dosage form, each unit containing from 0.10 g to 1.00 g active ingredient.

11. A method of inhibiting platelet aggregation in mammals which comprises administering an effective amount of a composition comprising a compound of claim 1 and a suitable pharmaceutically acceptable carrier.

12. A method of treating or inhibiting thrombosis in mammals which comprises administering to a mammal in need of treatment an effective amount of a composition comprising a compound of claim 1 and a suitable pharmaceutically acceptable carrier.

* * * * *

Consumer and Corporate Affairs Canada

(11) (A) No. 1,194,875
(45) ISSUED: October 8, 1985
(52) Class 260-246.1
Class reference 260-266.3;
260-276.1

(51) Int. Cl.[4] C07D 495/04
(19) (CA) CANADIAN PATENT (12)
(54) Process for the preparation of thieno[3,2-c]pyridine derivatives and their derivatives

(72) Daniel Aubert
Claude Ferrand
Jean-Pierre Maffrand
France

(73) Assignee: Sanofi, France

(21) Application No.: 432,079
(22) Filed: July 8, 1983
(30) Priority Date: France (82 12 599) July 13, 1982

CLAIMS 20 – NO DRAWINGS

Canada

Distributed by the Patent Office, Ottawa
CCA-275 (11-82)

DEFENDANT'S EXHIBIT
DTX-1235

All Languages Ltd

S9

This invention relates to a process for the preparation of thieno[3,2-c]pyridine and to thieno[3,2-c]pyridine derivatives obtained by this process. These thieno[3,2-c]pyridine derivatives have therapeutic applications. The new derivatives, according to the invention, have the following formula:

[Refer to original text for chemical formula.]

(I)

in which Y may represent the OH hydroxyl or the OR group, in which R is a straight or branched lower alkyl radical, or Y represents a group

[Refer to original text for chemical formula.]

in which R_1 and R_2 are each, independently of each other, hydrogen or a straight or branched lower alkyl group; or R_1 and R_2 form together and with the nitrogen atom to which they are attached a heterocycle which may include a second heteroatom such as oxygen or nitrogen, wherein the latter may be substituted by a lower alkyl or benzyl radical which may be substituted; and X represents hydrogen, a halogen or a lower alkyl radical.

These compounds include an asymmetrical carbon which may exist in the form of 2 enantiomers. The invention also concerns each of the enantiomers and their mixture.

The invention also includes the addition salts with pharmaceutically acceptable mineral or organic acids if Y represents the OR groups or

[Refer to original text for chemical formula.]

or with mineral bases if Y represents OH.

The lower alkyl radical refers to a C_1-C_4 saturated hydrocarbon chain.

The invention also relates to a process for the preparation of compounds of formula (I) as defined above, wherein the esters of the invention, in which Y represents an OR group as defined above, are prepared by condensation of 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine, having the following formula:

[Refer to original text for chemical formula.]

(II)

with an α-chlorophenyl acetate having the following formula

[Refer to original text for chemical formula.]

(III)

All Languages Ltd
S10

in which R and X have the above-defined meanings. Acids of formula (I), in which Y represents the OH hydroxyl, are obtained by saponification.

To prepare the amides, in which Y represents a group

[Refer to original text for chemical formula.]

in which R_1 and R_2 have the above-defined meanings or even some esters of formula (I), the acid of formula (I)(R=OH) is reacted, after activation, if required, either with the amine

[Refer to original text for chemical formula.]

or with the alcohol R-OH.

The α-halogenated esters of formula (III) are prepared using known methods (E.L. ELIEL, M.T. FISK and T. PROSSER, Organic Syntheses, Coll. Vol. IV, J. WILEY and SONS, Inc. New York, 1963, p. 169).

Although it is entirely possible to obtain all the esters of formula (I) by the reaction between the compounds of formulae (II) and (III), it is preferable, for economic reasons, to prepare certain higher esters of formula (I) from the acid of formula (I) and alcohol (R-OH).

The condensation of tetrahydro-thieno-pyridine with the ester of formula (III) is effected in the presence of an alkali metal carbonate, such as potassium carbonate, for example, in an inert solvent, such as dimethylformamide, tetrahydrofuran or 1,2-dimethoxy ethane, at temperatures between 60°C and the boiling point of the solvent.

The saponification of the ester of formula (I), in which R is methyl or ethyl, is effected by an alkali metal hydroxide such as sodium or potassium hydroxide in a hydroalcoholic solvent, at temperatures between room temperature and the boiling point of the solvent.

Activation of the acid of formula (I) may be obtained by treatment with ethyl chloroformate in the presence of a slight excess of triethylamine at temperatures between –5°C and 0°C in an inert solvent such as chloroform, 1,2-dimethoxy ethane or tetrahydrofuran.

A mixed anhydride having the following formula:

[Refer to original text for chemical formula.]

(IV)

is formed, and if treated in situ with a slight excess either of alcohol or amine, at temperatures between 10°C and room temperature, the esters or amides of formula (I) will be formed respectively.

The activation of the acid of formula (I) may also be obtained in different ways: the amides of formula (I) were also thus prepared by condensing the acid (I) with the amine

All Languages Ltd
S11

[Refer to original text for chemical formula.]

in the presence of dicyclohexycarbodiimide in solution in 1,2-dichloro-ethane.

The esters of formula (I) may also be obtained in the conventional manner by condensing the corresponding acid and alcohol (ROH) in the presence of hydrochloric gas or thionyl chloride.

The following non-limiting examples are given to illustrate the invention.

EXAMPLE 1

Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate (R=-CH_3; X=2-Cl) derivative No. 1

31.47 g (0.144 mole) of methyl 2-chloro-o.chlorophenylacetate and 19.82 g (0.144 mole) of potassium carbonate are added to a 20-g (0.144 mole) solution of 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in 200 ml of dimethylformamide. The solution is then heated for four hours at 90°C. The reaction mixture is cooled to room temperature, the mineral salts are filtered and the solvent is evaporated. The residue is taken up in water and then extracted with ethylic ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated, to give a yellow oil, which is purified by means of its hydrochloride. White crystals: M.p.=130°-140°C (ethyl acetate, isopropanol). Yield: 45%.

EXAMPLE 2

Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetate (R=-CH_3; X=H) derivative No. 2

This compound is prepared by the same procedure described in Example 1, by alkylation of the 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine with methyl 2-chloro-phenylacetate. Hydrochloride; white crystals: M.p.=200°C (ethanol). Yield: 50%.

EXAMPLE 3

Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.fluorophenylacetate (R=-CH_3; X=2-F) derivative No. 3

This compound is prepared by the same procedure described in Example 1, by alkylation of the 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine with methyl 2-chloro-o.fluorophenylacetate. Hydrochloride; white crystals: Softening point=100°C. Yield: 76.5%.

EXAMPLE 4

Ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.methylphenylacetate. (R=-CH_2-CH_3; X=2-CH_3) derivative No. 4

All Languages Ltd

This compound is prepared by the same procedure described in Example 1, by alkylation of the 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine with ethyl 2-chloro-o.methylphenylacetate. Bisulphate: white crystals: M.p.=188°-190°C (iscpropanol). Yield: 54%.

EXAMPLE 5

α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid. (Y=OH; X=2-Cl) derivative No. 5

A mixture of 157.9 g of ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate and 100 ml of a 30% sodium hydroxide solution in 600 ml of ethanol is heated under reflux for 2 hours 30 minutes. After evaporation of the ethanol, the mixture is acidified with glacial acetic acid and extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulphate and then evaporated. After recrystallization in water, the product is isolated in monohydrate form. White crystals: Softening point = 125°C (water). Yield: 46%.

EXAMPLE 6

α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetic acid. (Y=OH; X=H) derivative No. 6

This compound is prepared by the procedure described in Example 9 by saponification of ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetate. The product is purified by means of its sodium salt. White crystals: M.p. 210°-215°C (ethanol, methanol). Yield: 74%.

EXAMPLE 7

n-Propyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate (R=-CH_2-CH_2-CH_3; X=2-Cl) derivative No. 7

A stream of hydrochloric gas is bubbled through a 10-g (0.0306 mole) solution of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate (Example 5) for 12 hours in 100 ml of n-propanol, which is refluxed. The mixture is evaporated and the residue is taken up in water, basified with sodium bicarbonate and extracted with ethylic ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated to give a yellow oil, which is purified by means of its bisulphate. White crystals: M.p.=146°C (crude). Yield: 78%.

EXAMPLE 8

n-Butyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate (R=-CH_2-CH_2-CH_2-CH_3; X=2-Cl) derivative No. 8

This compound is prepared by the procedure described in Example 5 by esterification of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate (Example 5) with n-butanol. Purified using the bisulphate; white crystals: M.p =155°C. Yield: 79.5%.

All Languages Ltd

EXAMPLE 9

Isopropyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate (R=-CH[refer to original text for formula]; X=2-Cl) derivative No. 9

2 ml of thionyl chloride are added dropwise to a 1-g (0.0031 mole) suspension of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate (Example 5) in 20 ml of isopropanol cooled to –10°C. The reaction mixture is then refluxed for 6 hours. After evaporation, the residue is taken up in water, basified with sodium bicarbonate and extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulphate and evaporated. A colourless resin is collected and purified using its bisulphate.
White crystals: Softening point=140°-150°C. Yield: 44%.

EXAMPLE 10

Ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate. (R=-CH_2-CH_3; X=2-Cl) derivative No. 10

4.86 ml (0.051 mole) of ethylchloroformate are added dropwise to a 15-g (0.046 mole) solution of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate (Example 5) and 7.12 ml (0.051 mole) of triethylamine in 150 ml of chloroform, cooled to a temperature between –5°C and 0°C. The mixture is then allowed to return to room temperature and is stirred for 30 minutes. The reaction mixture is then cooled to a temperature of around 10°C and 30 ml of ethanol are added dropwise. The reaction mixture is stirred at room temperature for one night and is then washed with water. The organic phase, dried over sodium sulphate, is evaporated to give a colourless oil, which is purified by means of its hydrobromide.
White crystals: M.p.=180°C. Yield: 94%.

EXAMPLE 11

N,N-Dimethyl [α-(4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl)]-o.chlorophenylacetamide

(Y=-N[refer to original text for formula]; X=2-Cl) derivative No. 11.

9.72 ml (0.102 mole) of ethyl chloroformate are added dropwise to a 30-g (0.092 mole) solution of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate and 14.24 ml (0.102 mole) of triethylamine in 300 ml of chloroform, cooled to a temperature between –5° and 0°C. The mixture is then allowed to return to room temperature and the reaction mixture is stirred for 30 minutes. The latter is then cooled to a temperature of around 10°C and 4.57 ml (0.102 mole) of dimethylamine are added dropwise to 60 ml of chloroform and the mixture is stirred at room temperature for one night. Water is added, the mixture is decanted, and the organic phase is dried over sodium sulphate and evaporated. A colourless resin is collected, which then crystallizes.
White crystals: M.p.=95°-100°C (isopropylic ether). Yield: 49%.

EXAMPLE 12

All Languages Ltd

1-[(2-chlorophenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl-)acetyl]pyrrolidine

(Y=-N[refer to original text for symbol]; X=2-Cl) derivative No. 12.

This compound is prepared by the procedure described in Example 11 by condensing α-[4,5,6,7-tetrahydro-thieno[2,3-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate with pyrrolidine.
White crystals: M.p.=130°C (isopropylic ether). Yield: 61.5%.

EXAMPLE 13

1-[(2-chlorophenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl-)acetyl]morpholine

(Y=-N[refer to original text for symbol]; X=2-Cl) derivative No. 13.

2.67 g (0.031 mole) of morpholine are added to a 10-g (0.031 mole) solution of α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate and 13.3 g (0.064 mole) of dicyclohexylcarbodiimide in 100 ml of 1,2-dichloro ethane and the mixture is stirred at room temperature for one night. The mixture is evaporated, then taken up with 2N hydrochloric acid and ethylic ether. After filtering the dicyclohexylurea formed, the filtrate is decanted and the aqueous phase is basified with 2N sodium hydroxide, then extracted with methylene chloride. The organic phase is washed with water, dried over sodium sulphate and evaporated to give a yellow resin, which is purified by means of its hydrochloride hemihydrate.
White crystals: M.p.=215°-225°C (isopropanol). Yield: 71%.

EXAMPLE 14

1-[(2-chlorophenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl-)acetyl]piperidine

(Y=-N[refer to original text for symbol]; X=2-Cl) derivative No. 14.

This compound is prepared by the procedure described in Example 13 by condensing α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate with piperidine.
White crystals: M.p.=139°C (isopropanol). Yield: 51.5%.

The following compounds were prepared by the process described in example 11:

- [α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)]-o.chlorophenylacetamide. (Y=-NH_2; X=2-Cl) derivative No. 15.
White crystals: M.p.=126°-128°C (isopropylic ether-isopropanol).
Yield: 46%.

- 4-benzyl-1-[(2-chloro-phenyl)-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)acetyl]piperazine (Y=-N[refer to original text for formula]; X=2-Cl) derivative No. 16.
Oxalate: white crystals. M.p =178°C (ethanol).
Yield: 82.5%

All Languages Ltd

- N,N-dimethyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)]-o.fluorophenylacetamide (Y=-N[refer to original text for formula]; X=2-F) derivative No. 17.
Slightly yellowish powder; M.p.=125°C (isopropylic ether-isopropanol). Yield: 41%.

- N-methyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)]-o.chlorophenylacetamide. (Y=NH-CH_3; X=2-Cl) derivative No. 18.
White crystals: M.p.=137°C (isopropanol).
Yield: 85.5%.

- N-butyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)]-o.chlorophenylacetamide. (Y=-NH-$(CH_2)_3$-CH_3; X=2-Cl) derivative No. 19.
White crystals: M.p.=101°C (isopropylic ether).
Yield: 65%.

- N,N-dimethyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)]phenylacetamide. (Y=-N[refer to original text for formula]; X=H) derivative No. 20.
White crystals: M.p.=138°C (isopropylic ether).
Yield: 39%

- N,N-dimethyl[α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)]-o.methylphenylacetamide. (Y=-N[refer to original text for formula]; X=2-CH_3) derivative No. 21.
White crystals: M.p.=119°C (hexane).
Yield: 15%

The pharmacological and toxicological results reported below demonstrate the properties of the derivatives of the invention both in terms of toxicity and tolerance, and the activity levels of the derivatives, especially their inhibiting action on blood-platelet aggregation and anti-thrombotic activity.

Thus, the purpose of the invention is to obtain a drug having, in particular, an inhibiting action on blood-platelet aggregation and anti-thrombotic action, wherein the active ingredient is a derivative of formula (I) or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid if Y represents the OR groups or $-NR_1R_2$, and with a mineral base if Y is OH.

TOXICOLOGICAL INVESTIGATION

The compounds of the invention exhibit an excellent tolerance and a low toxicity.

In addition, the tests carried out on acute, chronic, sub-chronic and delayed toxicity in various animal species showed no local or general reaction, no disturbances or abnormalities in the biochemical, macroscopic and microscopic examinations performed during this experiment.

All Languages Ltd

PHARMACOLOGICAL INVESTIGATION

1) Inhibiting action on blood-platelet aggregation

This experiment was performed on rats. The compound to be tested was administered orally in the form of a suspension in gum Arabic to the rats over a 3-day period, 48 hours, 24 hours and 2 hours before taking a 4-ml blood sample from the animals using Renaud's method from their jugular veins under anesthetic. The citrated blood was used in the aggregation determinations.

a) Determination of A.D.P.-induced blood-platelet aggregation

2 ml of citrated blood were poured quickly into a small beaker placed in a magnetic stirrer, fitted with a magnetic bar. After a few seconds of stirring, 0.4 ml of a solution containing 0.66 ug of adenosine-diphosphate (ADP) per ml was placed in the beaker. After 90 seconds of stirring, two 0.5-ml samples of blood were taken:

- the first was mixed with 0.5 ml of an EDTA-formol solution,
- the second was mixed with 0.5 ml of an EDTA only solution.

The purpose of adding EDTA formol is to stabilize the blood and thus to fix the aggregation, whereas EDTA alone causes disaggregation of all the platelet clusters.

After leaving the mixtures to rest for 10 minutes and centrifuging the two mixtures at low speed for 5 minutes in order to separate the red corpuscles, the supernatant platelet-rich plasma (PRP) was removed, diluted and a platelet count was made.

The intensity of the aggregation was determined by the following ratio:

$$\frac{\text{number of platelets in EDTA-formol}}{\text{number of platelets in EDTA}} \times 100 = \text{percentage of non-aggregated platelets.}$$

The blood-platelet aggregation inhibiting action of the product tested improves as the ratio approaches 100.

The results showing the mean percentage of non-aggregated platelets in groups of 5 rats (treated and reference groups) are shown in Table I.

All Languages Ltd

TABLE I: ADP TEST

PRODUCT	DOSAGE mg/kg	ROUTE	RESULT
Reference group		P.O.	16±4
Derivative No. 1	3 x 25	-	94±3
Reference group		-	20±11
Derivative No. 1	3 x 5	-	82±11
Reference group		-	23±15
Derivative No. 1	3 x 2.5	-	56±17
Reference group		-	8±0
Derivative No. 10	3 x 25	-	66±2
Derivative No. 10	3 x 12.5	-	49±11
Reference group		-	8±1
Derivative No. 10	3 x 10	-	24±5
Reference group		-	11±0
Derivative No. 9	3 x 60	-	65±7
Reference group		-	13±3
Derivative No. 4	3 x 100	-	89±1
Reference group		-	3±1
Derivative No. 4	3 x 100	-	89±4
Reference group		-	4±0
Derivative No. 2	3 x 100	-	72±12
Reference group		-	4±0
Derivative No. 12	3 x 100	-	27±5
Reference group		-	2±0
Derivative No. 17	3 x 100	-	11±3
Derivative No. 20	3 x 100	-	4±1
Reference group		-	18±1
Derivative No. 6	3 x 100	-	22±4

b) Determination of collagen-induced blood-platelet aggregation

0.10 ml of a solution containing 10 µg of collagen per ml was added to 1.5 ml of citrated blood. With the mixture being stirred, the platelets were counted continually.

The reduction of the number of free platelets over time was continuously measured and a curve was plotted showing the initial aggregation rate.

The results, representing mean values determined in each group of 5 rats (treated and reference groups), are shown in Table II.

TABLE II: COLLAGEN TEST

PRODUCT	DOSAGE mg/kg	ROUTE	RESULT
Reference group		P.O.	3.12±0.47
Derivative No. 1	3 x 25	-	0.14±0.03
Reference group		-	2.17±0.64
Derivative No. 1	3 x 5	-	0.19±0.04
Reference group		-	5.00±1.02
Derivative No. 1	3 x 2.5	-	0.60±0.20
Reference group		-	3.92±0.63
Derivative No. 10	3 x 25	-	0.16±0.07
Derivative No. 10	3 x 12.5	-	0.54±0.12
Reference group		-	2.00±0.35
Derivative No. 7	3 x 100	-	0.66±0.18
Derivative No. 8	3 x 100		0.86±0.18
Reference group		-	2.25±0.32
Derivative No. 9	3 x 60	-	0.11±0.01
Reference group		-	3.41±0.55
Derivative No. 4	3 x 100	-	0.12±0.02
Reference group		-	4.73±0.55
Derivative No. 4	3 x 100	-	0.30±0.02
Reference group		-	5.00±1.06
Derivative No. 2	3 x 100	-	0.51±0.18
Reference group		-	2.25±0.32
Derivative No. 11	3 x 100	-	0.83±0.02
Reference group		-	2.77±0.32
Derivative No. 14	3 x 100	-	1.89±0.13
Reference group			3.99±0.40
Derivative No. 17	3 x 100	-	2.22±0.10
Reference group		-	5.01±0.79
Derivative No. 21	3 x 100	-	3.04±0.22
Reference group			11.35±1.01
Derivative No. 18	3 x 100		10.82±0.81

c) Determination of bleeding time

The study of the blood-platelet aggregation inhibiting action also concerned the action of the compound of the invention on bleeding time.

The method used is an adaptation of the method of L. STELLA, M.B. DONATI and G. de GAETANO, Thromb. Res., 1975, 7, 709-716.

The experiment was performed on rats. The compound to be tested was administered to the animals per os in suspension in 10 ml/kg of a 5% aqueous solution of gum Arabic, 65 hours, 41 hours and 17 hours prior to determination. After anesthetizing the animals with pentobarbital, their tails were cut 5 mm from the ends. The blood was carefully sponged at 15-second intervals, taking care not to touch the wound.

Hemostasis was reached when the bleeding stopped for one minute.

The results representing mean bleeding times in seconds, determined in each group of 5 rats (reference and treated groups), are given in Table III. Times longer than 1,200 seconds (20 minutes) were not counted.

TABLE III: BLEEDING TIME

PRODUCT	DOSAGE mg/kg	ROUTE	RESULT
Reference group		P.O.	600
Derivative No. 10	3 x 200	-	>1,200
Derivative No. 2	3 x 200	-	>1,200
Reference group		-	420
Derivative No. 1	3 x 25	-	>1,200
Derivative No. 1	3 x 5	-	1,080
Reference group		-	435
Derivative No. 1	3 x 12.5	-	>1,200
Reference group		-	780
Derivative No. 3	3 x 200	-	>1,200
Reference group		-	600
Derivative No. 18	3 x 200		>1,200
Reference group		-	600
Derivative No. 12	3 x 200	-	>1,200

2) Anti-thrombotic Activity

This activity was studied by the silk thread experimental thrombosis method.

All Languages Ltd

The principle of this study is an adaptation of the experimental thrombosis method using cardiopulmonary by-pass described by TERUHIKO UMETSU and KAZUKO SANAI (THROMB. HAEMOST., 39, 1, 1978).

Once anesthetized by an intraperitoneal injection of pentobarbital, the rats' left jugular veins and right external carotid arteries were uncovered.

The arteriovenous shunt consists of a central catheter and two lateral catheters; a white raw silk thread is inserted in the central part and circulation is restored for 20 minutes. After stopping circulation by clamping, the thread is gently withdrawn and weighed immediately. As the average weight of a wet silk thread was previously determined, the weight of the thrombus is determined by evaluating the difference.

The treatment is applied 48 hours, 24 hours and 2 hours before the start of blood flow in the shunt by oral administration of the compound to be tested in suspension in 10 ml/kg of 5% gum Arabic, while only the 5% gum Arabic solution is administered to the reference group.

The results showing the weight of the thrombus in mg are given in Table IV.

TABLE IV: ANTI-THROMBOTIC ACTIVITY

PRODUCT	DOSAGE mg/kg	ROUTE	WEIGHT OF THROMBOSIS IN mg	PERCENTAGE VARIATION
Reference group		P.O.	38.56±2.42	
Derivative No. 8	3 x 200	-	29.99±3.05	-22
Reference group		-	42.65±3.30	
Derivative No. 3	3 x 200	-	2.60±0.24	-94
Reference group		-	36.24±2.05	
Derivative No. 1	3 x 25	-	6.56±0.51	-82
Derivative No. 1	3 x 12.5	-	15.98±1.81	-56
Reference group		-	40.86±2.02	
Derivative No. 1	3 x 5	-	27.7±2.82	-32
Reference group		-	40.68±1.74	
Derivative No. 2	3 x 200	-	8.42±3.28	-79
Derivative No. 10	3 x 200	-	5.89±0.99	-86
Reference group		-	35.76±1.76	
Derivative No. 11	3 x 200	-	21.38±2.92	-40

The toxicological and pharmacological investigations reported above demonstrate the low toxicity of the compounds of the invention, as well as their excellent tolerance and their inhibiting properties on blood-platelet aggregation, and their anti-thrombotic activity, which make them very useful in human and veterinary therapeutic applications.

All languages ltd

The drug of the invention may be orally administrated in the form of tablets, coated tablets, capsules, drops, granules or syrup. The drug can also be provided in the form of suppositories for rectal administration or in the form of solution for injection for parenteral administration.

Each unit dose contains advantageously from 0.005 g to 0.250 g of a derivative of the invention, the daily dosage regimen varying within a range from 0.005 g to 1.00 g of active ingredient according to the age of the patient and the severity of the disease to be treated.

Non-limiting examples of pharmaceutical formulations of the drug of this invention are given below.

1. Tablets
Derivative No. 1 0.050 g
Excipient: lactose, icing sugar, rice starch, alginic acid, magnesium stearate.

2. Coated Tablets
Derivative No. 10 0.100 g
Excipient: magnesium stearate, corn starch, gum Arabic, shellac, white sugar, glucose, white wax, carnauba wax, paraffin, new cochinealin.

3. Capsules
Derivative No. 17 0.100 g
Excipient: magnesium stearate, corn starch, lactose.

4. Solution for Injection
Derivative No. 4 0.075 g
Isotonic solvent sufficient to make 3 ml

5. Suppositories
Derivative No. 21 0.100 g
Semi-synthetic triglycerides sufficient to make 1 suppository.

All Languages Ltd
S22

The findings of the invention, for which an exclusive property and privilege right is claimed, are defined as follows:

1. A process for the preparation of derivatives of general formula (I):

[Refer to original text for chemical formula.]

(I)

in which Y may represent either a hydroxyl radical or an -OR group radical, in which R is a straight or branched lower alkyl radical, or Y represents a radical of the formula:

[Refer to original text for chemical formula.]

in which either R_1 and R_2, identical or different, represent a hydrogen atom or a straight or branched lower alkyl group; or R_1 and R_2 form together and with the nitrogen atom to which they are attached a heterocycle which may or may not include a second heteroatom chosen from the group containing oxygen and nitrogen, wherein the latter may be substituted by a lower alkyl or benzyl radical which may or may not be substituted; and X represents a hydrogen or halogen atom, or a lower alkyl radical; and their the addition salts with pharmaceutically acceptable mineral or organic acids if Y represents a radical of the -OR formula or of the $-NR_1R_2$ formula; R, R_1 and R_2 having the above-defined meanings, or with mineral bases if Y represents a hydroxyl radical; as well as the 2 enantiomers or their mixture of these compounds of formula (I); wherein:

- either, in order to prepare the esters of formula (I), in which Y represents a radical of the –OR formula, in which R has the above-defined meaning, and X has the above-defined meaning, the 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine of formula (II) is condensed:

[Refer to original text for chemical formula.]

(II)

on a α-chlorophenylacetate of formula (III):

[Refer to original text for chemical formula.]

(III)

in which R and X have the above-defined meanings, then the derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action;

- or, in order to prepare the acid of formula (I) in which Y represents a hydroxyl radical and X has the above-defined meaning, the ester of formula (I), in which Y represents a radical of the –OR formula in which R and X have the above-defined meanings, is saponified, then the derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action:

All Languages Ltd
S23

- or, in order to prepare the compounds of formula (I), in which X has the above-defined meaning and Y represents a radical of the –OR formula, in which R has the above-defined meaning, or a radical of the $-NR_1R_2$ formula, in which R_1 and R_2 have the above-defined meanings, the acid of formula (I), in which X has the above-defined meaning and Y represents a hydroxyl radical, may or may not be activated, is reacted with either an alcohol of the H-OR formula, in which R has the above-defined meaning, or with an amine of the $H-NR_1R_2$ formula, in which R_1 and R_2 have the above-defined meanings, then the corresponding derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action.

2. Process according to claim 1, wherein the condensation reaction between the thieno-pyridine of formula (II) and the ester of formula (III) is effected in the presence of an alkali metal carbonate, in an inert solvent, at temperatures between 60°C and the boiling point of the solvent.

3. Process according to claim 1, wherein the saponification of the ester of formula (I), in which R is methyl or ethyl, is effected by an alkali metal hydroxide in a hydroalcoholic solvent, at temperatures between room temperature and the boiling point of the solvent.

4. Process according to claim 1, wherein the activation of the acid of formula (I) is obtained by ethyl chloroformate in the presence of triethylamine at temperatures between –5°C and 0°C in an inert solvent.

5. Process according to claim 1, wherein the activation of the acid of formula (I) is obtained by ethyl chloroformate in the presence of triethylamine at temperatures between –5°C and 0°C in a solvent chosen in the group containing chloroform, 1,2-dimethoxy ethane or tetrahydrofuran.

6. Process according to claim 1, wherein the activation of the acid of formula (I) for the preparation of amides was effected by dicyclohexycarbodiimide.

7. Process according to claim 1, wherein the activation of the acid of formula (I) for the preparation of esters is effected by a current of hydrochloric gas or thionyl chloride.

8. Process according to claim 1, for the preparation of methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate, wherein the 4,5,6,7-tetrahydro thieno[3,2-c]pyridine is condensed over the methyl 2-chloro-o.chlorophenylacetate, and the derivative sought, which is isolated, is obtained.

9. Process according to claim 1, for the preparation of methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetate, wherein the 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine is condensed over the methyl 2-chloro-phenylacetate, and the derivative sought, which is isolated, is obtained.

10 Process according to claim 1, for the preparation of methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.fluorophenylacetate, wherein the 4,5,6,7-tetrahydro-thieno[3,2-

All Languages Ltd

c]pyridine is condensed over the methyl 2-chloro-o.fluorophenylacetate, and the derivative sought, which is isolated, is obtained.

11. Process according to claim 1, for the preparation of isopropyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate, wherein the α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate is reacted with isopropanol in the presence of thionyl chloride, and the derivative sought, which is isolated, is obtained.

12. Process according to claim 1, for the preparation of ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o-chlorophenylacetate, wherein the α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate is activated by the action of the ethyl chloroformate in the presence of triethylamine, which is reacted by this acid activated with ethanol, and the derivative sought, which is isolated, is obtained.

13. Process according to claim 1, for the preparation of N,N-dimethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetamide, wherein the α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetic acid monohydrate is activated by the action of the ethyl chloroformate in the presence of triethylamine, which is reacted by this acid activated with dimethylamine, and the derivative sought, which is isolated, is obtained.

14. Derivatives of general formula (I):

[Refer to original text for chemical formula.]

(I)

in which Y may represent either a hydroxyl radical or an -OR group radical, in which R is a straight or branched lower alkyl radical, or Y represents a radical of the formula:

[Refer to original text for chemical formula.]

in which R_1 and R_2, identical or different, represent a hydrogen atom or a straight or branched lower alkyl group; or R1 and R2 form together and with the nitrogen atom to which they are attached a heterocycle which may or may not include a second heteroatom chosen from the group containing oxygen and nitrogen, wherein the latter may be substituted by a lower alkyl or benzyl radical which may or may not be substituted; and X represents a hydrogen or halogen atom, or a lower alkyl radical; and their addition salts with pharmaceutically acceptable mineral or organic acids if Y represents a radical of the -OR formula or of the $-NR_1R_2$ formula; R, R_1 and R_2 having the above-defined meanings, or with mineral bases if Y represents a hydroxyl radical; as well as the 2 enantiomers or their mixture of these compounds of formula (I); each time they are obtained by the process of claim 1 or its manifest chemical equivalents.

15. Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate, each time it is obtained by the process of claim 8 or its manifest chemical equivalents.

16. Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-phenylacetate, each time it is obtained by the process of claim 9 or its manifest chemical equivalents.

All Languages Ltd
S25

17. Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.fluorophenylacetate, each time it is obtained by the process of claim 10 or its manifest chemical equivalents.

18. Isopropyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetate, each time it is obtained by the process of claim 11 or its manifest chemical equivalents.

19. Ethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o-chlorophenylacetate, each time it is obtained by the process of claim 12 or its manifest chemical equivalents.

20. N,N-dimethyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-o.chlorophenylacetamide, each time it is obtained by the process of claim 13 or its manifest chemical equivalents.

All languages ltd

ABSTRACT

The invention concerns a process for the preparation of derivatives of general formula (I):

[Refer to original text for chemical formula.]

(I)

in which Y may represent either an OH hydroxyl or an -OR group, in which R is a straight or branched lower alkyl radical, or Y represents a radical of the formula:

[Refer to original text for chemical formula.]

in which R_1 and R_2 are each, independently of each other, hydrogen or a straight or branched lower alkyl group; or R_1 and R_2 form together and with the nitrogen atom to which they are attached a heterocycle which may or may not include a second heteroatom, such as oxygen or nitrogen, wherein the latter may be substituted by a lower alkyl or benzyl radical which may or may not be substituted; and X represents hydrogen or halogen, or a lower alkyl radical; and their addition salts with pharmaceutically acceptable mineral or organic acids if Y represents the OR groups or

[Refer to original text for chemical formula.]

or with mineral bases if Y represents OH, as well as the 2 enantiomers or their mixture. The invention also concerns the derivatives of formula (I) obtained by the implementation of this process. These derivatives of formula (I) are useful as inhibiting agents of blood-platelet aggregation and anti-thrombotic action.

All languages ltd

AFFIDAVIT

I, Florinda Lages, translator for ALL LANGUAGES LTD, of Toronto, in the Province of Ontario, make oath and say:

1. I understand both the French and the English languages;

2. I have carefully compared the annexed translation from French into English with Canadian Patent Number 1,194,875, issued on October 8, 1985; and

3. The said translation, done by me, is, to the best of my knowledge and ability, a true and correct translation of the said document in every respect.

SWORN before me at the City of)
Toronto, this 6th day of May)
A.D. 2002.)
)
)
A Notary Public in and for the)
Province of Ontario.)

MAURICE PENZO, Notary Public, City of Toronto, limited to the attestation of instruments and the taking of affidavits, for All Languages Ltd.
Expires December 12, 2004

All Languages Ltd

S28

United States Patent [19]

Badorc et al.

[11] **Patent Number: 4,847,265**

[45] **Date of Patent: Jul. 11, 1989**

[54] **DEXTRO-ROTATORY ENANTIOMER OF METHYL ALPHA-5 (4,5,6,7-TETRAHYDRO (3,2-C) THIENO PYRIDYL) (2-CHLOROPHENYL)-ACETATE AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING IT**

[75] Inventors: **Alain Badarc, Roquettes; Daniel Fréhel, Toulouse**, both of France

[73] Assignee: **Sanofi**, France

[21] Appl. No.: **155,550**

[22] Filed: **Feb. 12, 1988**

[30] **Foreign Application Priority Data**

Feb. 17, 1987 [FR] France 87 02025
Nov. 27, 1987 [FR] France 87 16516

[51] **Int. Cl.**[4] **A61K 31/44; C07D 495/04**
[52] **U.S. Cl.** **514/301; 546/114**
[58] **Field of Search** 546/114; 514/301

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,529,596 7/1985 Aubert et al. 546/115

FOREIGN PATENT DOCUMENTS

0099802 7/1983 European Pat. Off. .

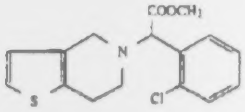
OTHER PUBLICATIONS

Fieser et al., Advanced Org. Chem.-Reinhold Publishing Co., N.Y., (1961), pp. 85-88.

Primary Examiner—Mary C. Lee
Assistant Examiner—Bernard I. Dentz
Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

The present invention relates to the dextro-rotatory enantiomer of Formula



and its pharmaceutically acceptable salts with platelet aggregation inhibiting activity.

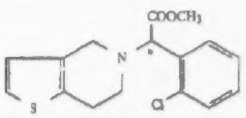
The invention also relates to a process for the preparation of this compound starting from the racemate and the pharmaceutical compositions containing it.

7 Claims, No Drawings

DEXTRO-ROTATORY ENANTIOMER OF METHYL ALPHA-5 (4,5,6,7-TETRAHYDRO (3,2-C) THIENO PYRIDYL) (2-CHLOROPHENYL)-ACETATE AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING IT

The present invention relates to the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate, a process for its preparation and pharmaceutical compositions containing it.

The compound of the invention corresponds to the following formula (I):



(I)

in which the C* is an asymmetric carbon atom. In fact, this formula represents both the dextro-rotatory molecule claimed as well as its levo-rotatory enantiomer. The racemic mixture corresponding to this formula was described in the French patent application published under the No. 2 530 247. Hereafter the dextro-rotatory enantiomer claimed according to the invention will be designated by I_d and the levo-rotatory enantiomer by I_l.

It is known that the optical rotatory power of a compound depends on the solvent in which it is measured and on its concentration in this solvent. The optical rotatory power of the dextro-rotatory isomer according to the invention is positive in methanolic solution.

In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers.

The invention also relates to the addition salts of the compounds of formula (I_d) with pharmaceutically acceptable mineral or organic acids.

The compound (I_d) is an oil whereas its hydrochloride exists as a white powder. The oily products are usually difficult to purify and it is preferable to use for the preparation of pharmaceutical compositions crystalline products which can usually be purified by recrystallization.

However, it has been observed in the present case that some of the salts of compound (I_d) usually precipitate in an amorphous form and/or that they are hygroscopic, a property which makes them difficult to handle on an industrial scale. Thus, the salts of carboxylic acid and sulfonic acids classically used in pharmacy have been prepared, acids such as acetic, benzoic, fumaric, maleic, citric, tartaric, gentisic, methane-sulfonic, ethanesulfonic, benzenesulfonic and laurylsulfonic acids as well as the salts of dobesilic acid (m.p. = 70° C.) and para-toluenesulfonic acid (m.p. = 51° C.), the purification of which proved to be difficult.

Among the mineral and organic acid salts of the dextro-rotatory isomer of the compound of Formula (I_d) salts have been found which crystallize easily, are not hygroscopic and are sufficiently water-soluble as to make their use as active medicinal principles particularly advantageous.

The present invention thus relates more particular to the hydrogen sulfate, the taurocholate and the hydr bromide of the dextro-rotatory enantiomer of meth alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (chlorophenyl)-acetate.

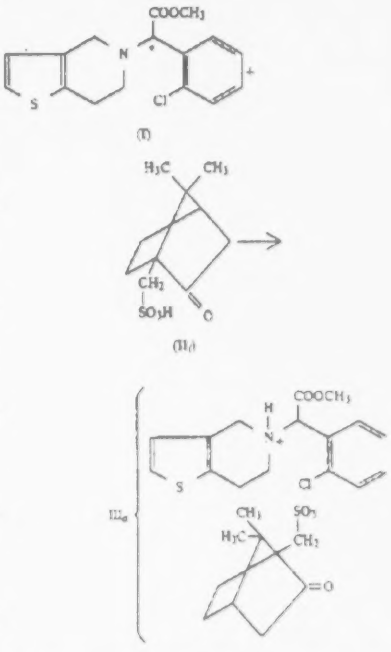
These salts are prepared in a standard manner by t action of the corresponding acid on the base in soluti in a solvent from which they precipitate spontaneous or after addition of a non-solvent of the salt.

The dextro-rotatory isomer of methyl alpha-5(4,5,6, tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-ac tate can be prepared by forming the salt of the racem compound with an optically active acid in a solve repeated recrystallizations of the salt until a product constant optical rotatory power is obtained, follow by the liberation of the dextro-rotatory isomer from salts by a base; if required, a salt is formed between t dextro-rotatory isomer and a pharmaceutically acce able acid.

The optically active acid may advantageously levo-rotatory camphor-10-sulfonic acid.

One and the same solvent may be used for salt form tion and recrystallization: acetone is ideally suited this case.

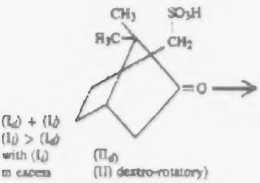
The chiral, levo-rotatory camphor-10-sulfonic acid Formula (II$_l$) is allowed to react in an inert solvent w the racemic mixture of Formula (I) according to t following reaction scheme:

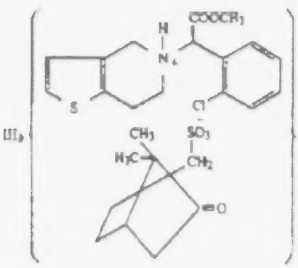


Salt formation may be carried out in solvents such alcohols, ketones, dimethylformamide. The salt prec tates spontaneously or is isolated by salting out or ev oration of the solvent. A mixture of two diastereoi mers of Formula (IIIa) is formed. By repeated recrys lizations from a solvent such as acetone the precipit

is enriched in the salt of the dextro-rotatory isomer of compound (I). After each recrystallization the optical rotatory power $[\alpha]_D^{20}$ of the precipitate is measured at 20° C. in methanol at a concentration varying between 1.5 and 2 g/100 mL When the $[\alpha]_D^{20}$ stops increasing the base of Formula (I_D) is liberated from the salt (IIIa) by the action of a base such as sodium or potassium hydrogen carbonate in aqueous media at temperatures varying between 5° C. and 20° C. Evaporation of the filtrate of the first recrystallization IV after the crystals of the precipitated salt (IIIa) have been filtered off, gives a mixture enriched in the salt of (I_l) enantiomer. The basification of this mixture of diastereoisomeric salts with a weak base such as sodium or potassium hydrogen carbonate in aqueous solution at temperatures varying between 5° C. and 20° C. leads to a mixture of the two enantiomers (I_d) plus (I_l) enriched in the levo-rotatory enantiomer (I_l).

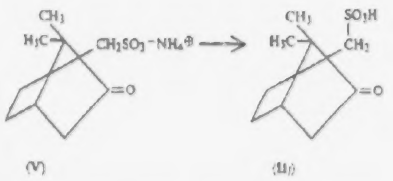
This mixture (I_d)+(I_l) enriched in enantiomer (I_l) is allowed to react with dextro-rotatory camphor-10-sulfonic acid which will be designated as (II_d) in a solvent according to the following reaction scheme:





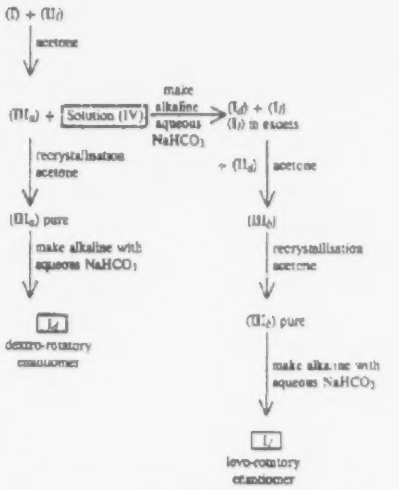
The crystalline mixture of diastereoisomeric salts (IIIb) obtained is recrystallized from acetone until the optical rotatory power $[\alpha]_D^{20}$ of the precipitate remains constant. As previously mentioned the optical rotatory power $[\alpha]_D^{20}$ of the diastereoisomeric salt (IIIb) is determined after each recrystallization.

The liberation of the stereoisomeric (I_l) from its salt is carried out in a standard manner, like that for compound (I_d). Levo-rotatory camphor-10-sulfonic acid (II_l) may be obtained from commercially available ammonium camphor-10-sulfonate of Formula (V) according to the reaction scheme:



An aqueous solution of the ammonium salt (V) is chromatographed on an Amberlite IRN-77 resin. After lyophilization of the eluate camphor-10-sulfonic acid of Formula (II_l) is recovered.

The entire sequence of the process is shown schematically below:



Each of the pure enantiomers (I_d) and (I_l) may be converted into a salt by means of the standard methods. for example, the hydrochlorides are prepared by the addition of a solution of hydrogen chloride gas in diethyl ether to a solution of (I_d) or (I_l) in diethyl ether.

DETERMINATION OF THE ENANTIOMERIC PURITY OF THE DEXTRO-ROTATORY (I_d) AND LEVO-ROTATORY (I_l) ENANTIOMERS

Two methods have been used:

- proton NMR spectroscopy with the addition of a chiral rare earth
- high pressure liquid chromatography using a chiral stationary phase.

(a) Proton NMR spectroscopy with the addition of a chiral rare earth The enantiomeric purity (optical purity) was determined by ^1H 60 MHz NMR spectroscopy in the presence of a rare earth chiral complex according to the method described by G. M. WHITESIDES et al. (J. Am. Chem. Soc. 1974, 96, 1038).

In the racemic product (I), the hydrogen attached to the asymmetric centre in the α position to the ester function appears as a singlet (chemical shift $\delta = 4.87$ ppm in $CDCl_3$ as solvent. The addition of the rare earth complex Eu(tfc)$_3$ [tris 3-(trifluoromethyl hydroxyme-

thylene)-d-camphorato europium (III)] to the probe containing a solution of the racemate (I) in $CDCl_3$ leads to the resolution of the initial singlet into two, well-separated singlets corresponding to the proton of each of the two enantiomers (I_d) and (I_l). When the molar ratio of rare earth complex/compound (I)=0.4, the separation between the two singlets is about 6 Hz.

With each of the two enantiomers prepared, (I_d) and (I_l), the same procedure was used as for the racemate (I). The smaller chemical shift corresponds to the proton of the dextro-rotatory enantiomer (I_d) and the larger chemical shift to the levo-rotatory enantiomer (I_l).

The precision of the method was determined by comparing the ^1H (60 MHz) NMR spectra obtained with and without addition of the rare earth complex for each of the two enantiomers (I_d) and (I_l) in the pure state or as mixtures containing increasing quantities of one of the enantiomers. It was observed that it was possible to detect easily more than 5% by weight of one enantiomer in the presence of the other.

(b) High pressure liquid chromatography using a chiral stationary phase The study was conducted with a liquid chromatograph HP-1084 using a UV detector at 215 nm. The chiral stationary phase was DEAE silica (10 microns) onto which was grafted alpha-1 acid glycoprotein (0.4×100 mm) (ENANTIOPAC R-LKB). The mobile phase consisted of an aqueous phosphate buffer mixture 8 mM (NaH_2PO_4/Na_2HPO_4) containing 0.1M of NaCl, adjusted to pH=7.4, and 15% of isopropanol (v/v). The flow rate was fixed at 0.3 ml/minute and the temperature of the column was maintained at 18°-20° C. Under these conditions, the dextro-rotatory enantiomer (I_d) has a retention time of 45 minutes and the levo-rotatory enantiomer (I_l) has a retention time of 35 minutes.

The precision of the determination of the optical purity of the two enantiomers was estimated by chromatographing each of the two enantiomers (I_d) and (I_l) prepared either alone or as a mixture containing increasing amounts of one of the enantiomers. It was observed that it was easy to detect:

2% (weight/weight) of enantiomer (I_d) in enantiomer (I_l)

4% (weight/weight) of enantiomer (I_l) in enantiomer (I_d).

Under these conditions it may be concluded that the optical purity of the two enantiomers (I_d) and (I_l) obtained according to the examples is at least equal to 96% for the dextro-rotatory enantiomer (I_d) and at least equal to 98% for the levo-rotatory enantiomer (I_l).

The following examples are non-restrictive and are presented to illustrate the present invention.

EXAMPLE I

Salts of dextro-rotary methyl-alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

(a) levo-rotatory camphor-10-sulfonic acid

A column of Amberlite IRN-77 resin is prepared and tested by passing 1N hydrochloric acid through it and then by washing this column of acidified resin abundantly with water. Levo-rotatory ammonium camphor-10-sulfonate is dissolved in a minimum of water and applied to the column of resin previously prepared. Elution is carried out with water. The eluted fractions containing the acid are lyophilized.

White crystals, m.p.=198° C.; $[\alpha]_D^{20}=-20.53$ (c=2.075 g/100 ml water).

(b) Camphor-10-sulfonic acid salt of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990 B).

32 g (0.0994 mole) of racemic methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate are dissolved in 150 ml of acetone. 9.95 g (0.0397 mole) of levo-rotat camphor-10-sulfonic acid monohydrate are added. The clear solution is left to stand at room temperature. After 48 hours some crystals have formed. The reaction mixture is concentrated to 50 ml and left to stand at room temperature for 24 hours. The crystals obtained are filtered off, washed with acetone and dried (yield: 55% on the basis of the starting racemate).

White crystals, m.p.=165° C., $[\alpha]_D^{20}=+24.67$ (c=1.58 g/100 ml; methanol).

The crystals obtained above are redissolved in the minimum of boiling acetone (50 ml). The crystals obtained after cooling are filtered off, washed with acetone and dried (yield: 88%).

White crystals, m.p.=165° C., $[\alpha]_D^{20}=+24.75$ (c=1.68 g/100 ml; methanol).

(c) Dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

12 g (0.022 mole) of the pure product obtained in (b) are dissolved in a minimum of water. After cooling to 5° C., the aqueous solution obtained is made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic extracts are dried over anhydrous sodium sulfate. On evaporation of the solvent a colorless oil is obtained (quantitative yield). Oil, $[\alpha]_D^{20}=+51.52$ (c=1.61 g/100 ml; methanol).

(d) The hydrochloride of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (dextro-rotatory) (SR 25990 A).

7 g (0.0228 mole) of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate are dissolved in 100 ml of diethyl ether. 30 ml of a solution of 1N HCl in diethyl ether are added and the crystals obtained are filtered off. The crystals are washed with diethyl ether and dried (yield: 94%).

White crystals, m.p.=117° C., $[\alpha]_D^{20}=+62.23$ (c=1.82 g/100 ml; methanol).

(e) The hydrogen sulfate of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990 C).

800 ml of a saturated aqueous solution of sodium bicarbonate are added to a suspension of 200 g of SR 25990 B in 800 ml of dichloromethane. After vigorous shaking, the organic phase is separated, dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is dissolved in 500 ml of ice-cold acetone and 20.7 ml of concentrated sulfuric acid (93.64%, d=1.83) are added drop-wise. The precipitate formed is isolated by filtration and washed with 1,000 ml of acetone, then dried in a vacuum oven at 50° C.

139 grams of analytically pure white crystals are thus obtained with a melting point of 184° C. Empirical formula $C_{16}H_{18}ClNO_2S.H_2SO_4$ $[\alpha]_D^{20}=+55.10$ (c=1.89 g/100 ml; methanol).

(f) The hydrochloride of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990D).

150 ml of an aqueous solution of sodium bicarbonate are added to a suspension of 20 g of SR 25990 B in 200

ml of dichloromethane. The residue obtained after separation of the organic phase, drying and evaporation of the solvent is dissolved in 150 ml of diethyl or diisopropyl ether, and 4.4 ml of a 48% (wt/v) aqueous solution of hydrobromic acid are added drop-wise. The precipitate formed is isolated. After drying, 14.4 g of crystals are obtained with a melting point of 111° C. (yield 99%).

13.4 g of these crystals are recrystallized from a mixture of isopropyl ether (100 ml) and isopropanol (150 ml) to give 10.2 g of analytically pure hydrobromide: m.p. = 140° C.; empirical formula: $C_{16}H_{16}ClNO_2S.HBr$ $[\alpha]_D^{20} = +59.23$ (c = 2.09 g/100 ml; methanol).

(g) The taurocholate of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990E).

The sodium salt of taurocholic acid is chromatographed on Amberlite IRN-77 resin by eluting with water. The fractions obtained are lyophilized.

3 g (0.0054 mole) of SR 25990B are treated with a saturated aqueous solution of sodium bicarbonate and the mixture is extracted with dichloromethane. The organic phase is separated, dried over sodium sulfate and evaporated to dryness. The free base obtained is taken up in 30 ml of isopropanol; 2.8 g (0.0054 mole) of taurocholic acid dissolved in 100 ml of isopropanol are added to this solution. The mixture is stirred overnight at room temperature, then evaporated to dryness. The residue solidifed on being triturated with ether. 3.5 g of beige crystals are obtained. m.p. = 120° C. $[\alpha]_D^{20} + = 39.53$ (c = 1.791 g/100 ml of methanol). $C_{16}H_{16}ClNO_2S.C_{26}H_{45}NO_7S$; C, H, N analyses in agreement with theory.

EXAMPLE 2

Salts of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

(a) Salt of d-camphor-10-sulfonic acid (SR 25989 B)

After separation of SR 25990 B in Example 1-b the solvent is evaporated from the acetone filtrate obtained.

The residue is taken up in water and diethyl ether. The ethereal phase is decanted. The aqueous phase is cooled to 5° C. and made alkaline with a saturated aqueous solution of sodium bicarbonate. The aqueous alkaline phase is extracted with diethyl ether. The ethereal extracts are pooled and dried over anhydrous sodium sulfate.

On evaporation of the solvent an oil is obtained which is purified by filtration through a bed of silica (eluant: diethyl ether). A colourless oil is recovered consisting of a mixture of about 65% of the levo-rotatory enantiomer and 35% of the dextro-rotatory enantiomer, proportions determined by means of ^1H (60 MHz) NMR spectroscopy after the addition of chiral, rare earth complex.

16.66 g (0.0517 mole) of the mixture thus obtained are dissolved in 70 ml of acetone. 7.77 g (0.0310 mole) of dextro-rotatory camphor-10-sulfonic acid monohydrate are added. The homogeneous mixture is left to stand overnight at room temperature. The crystals obtained are filtered off, washed with acetone and dried (yield: 44% based on the mixture).

The crystals obtained are dissolved in a minimum of refluxing acetone (60 ml). The precipitate obtained on cooling to room temperature is filtered off, washed with acetone and dried. White crystals, m.p. = 167° C., $[\alpha]_D^{20} = -24.85$ (c = 1.79 g/100 ml; methanol).

(b) Levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

11.3 g (0.0204 mole) of the camphor-10-sulfonate obtained in (a) are dissolved in a minimum of water. The aqueous solution obtained is cooled to 5° C. and made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic solution is dried and the solvent is evaporated. A colourless oil is isolated (quantitative yield).

Oil $[\alpha]_D^{20} = -50.74$ (c = 1.58 g/100 ml, methanol).

(c) The hydrochloride of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25989 A).

Prepared according to the method described in Example 1(d). Yield: 94%.

White crystals, m.p. = 117° C., $[\alpha]_D^{20} = -62.56$ (c = 1.80 g/100 ml; methanol).

(d) The hydrogen sulfate of levo-rotatory methyl-alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25989 C).

70 g (0.126 mole) of the camphor sulfonate SR 25989 B obtained are treated as described in (a) above with a saturated aqueous solution of sodium bicarbonate in the presence of dichloromethane. The organic phase is separated, dried over sodium sulfate and evaporated to dryness. The residue is taken up in 300 ml of acetone and 7.2 ml (0.126 mole) of concentrated sulfuric acid are added drop-wise. After being stirred the crystals formed are filtered off and washed with acetone. 47.8 g of white crystals are obtained. m.p. = 182° C. $[\alpha]_D^{20} = -51.61$ (c = 2.044 g/100 ml; methanol). The analysis (C,H,N) are in agreement with theory.

PHARMACOLOGICAL STUDY

The platelet aggregation inhibiting activity and the toxicity of these new compounds were compared to those of the racemic mixture described in the French Pat. No. 82.12599 (Publication No. 2 530 247).

A description will now be given of the results of this study which demonstrates another advantage of the invention, namely that the salts of the dextro-rotatory isomer have a better therapeutic index than the salt of the racemic mixture; in fact, the levo-rotatory isomer exhibits almost no platelet aggregation inhibiting activity and its toxicity is markedly higher than that of its dextro-rotatory homologue.

The platelet aggregation inhibiting activities and the antithrombotic activities of the compounds were studied in the rat by standard methods.

The activity on the aggregation of plates induced by ADP or collagen was determined ex-vivo.

The products dissolved in ethanol (200 mg/ml) and diluted in water containing gum arabic (5%-wt/v) were administered by the oral route to groups of five female rats of the CD-COBS strain, weighing 250-300 g, in amounts of 10 ml of suspension per kilogram two hours before blood samples were taken.

The blood samples were taken from animals anesthetized with diethyl ether by puncture of the abdominal aorta and placed over a 3.8% aqueous solution of sodium citrate (1 vol/9 volumes of blood). The platelet-rich plasma was then isolated by centrifugation at 200 g for 10 minutes.

Aggregation is induced by the addition of 2 µl of aggregating solution to 400 µl of platelet-rich plasma.

The aggregating solutions used were: a 500 μM aqueous solution of ADP marketed by Boehringer Mannheim (final concentration 2.5 μM), and a solution of collagen marketed by Sigma (type 1) at a concentration of 0.25 g/100 ml in 3% acetic acid (v/v) (final concentration 12.5 μg/ml).

The aggregation of the platelets was monitored as described in the method by G. V. R. Born in Nature 194, p. 927 (1967) using a Coultronics ® aggregometer at a temperature of 37° C. and agitation of 900 rpm.

For aggregation with ADP, the aggregometer generates a curve representing a platelet aggregation as measured by a change in optical density. The height of this curve is defined as the height of aggregation. The percentage of aggregation is the relation between the aggregation height measured and the height corresponding to 100% aggregation × 100. The percentage of inhibition is determined by the relation:

$$\frac{\text{Control aggregation height} - \text{produced aggregation height}}{\text{Control aggregation height}} \times 100$$

The results obtained for the aggregation with ADP for the hydrochloride of the racemic mixture (PCR 4099), the hydrogen sulfates of the dextro-rotatory (SR 25990 C) and levo-rotatory (SR 25989 C) isomers on the one hand, and for PCR 4099 and the hydrochlorides of the dextro-rotatory (SR 25990 A) and levo-rotatory (SR 25989 A) on the other, are shown in Table I; they demonstrate that the levo-rotatory isomer is inactive and that the dextro-rotatory isomer is at least as active as the racemate.

TABLE I

PRODUCT	DOSE mg/Kg P.O	QUANTITY of base administered		% INHIBITION	p**
			% AGGREGATION		
Controls			42.4 +/- 1.5		
PCR 4099	4.48	3.84	29.8 +/- 2.4	30	0.01
(racemate)	8.97	7.69	17.2 +/- 2.2	59	0.001
	17.9	15.38	11.1 +/- 2.3	74	0.001
SR 25989C	20	15.38	41.0 +/- 1.5	3	n.s
	40	30.76	37.1 +/- 1.7	13	n.s
SR 25990C	1.25	0.96	39.4 +/- 1.3	7	n.s
	2.5	1.92	28.4 +/- 2.3	33	0.01
	5	3.84	14.0 +/- 1.6	67	0.001
	10	7.69	8.5 +/- 1.6	80	0.001
Controls			33.8 +/- 2.3		
SR 25990E	10	3.84	9.6 +/- 3	72	0.001
	20	7.69	4 +/- 1.6	88	0.001
			AGGREGATION HEIGHT		
Controls			103 +/- 5		
PCR 4099	2.5	2.14	86 +/- 5	17	0.05
(racemate)	5	4.28	72 +/- 8	30	0.05
	12.5	10.71	32 +/- 9	69	0.001
SR 25989A	25	22.46	100 +/- 1	3	n.s
SR 25990A	2.5	2.25	67 +/- 7	35	0.01
	5	4.49	26 +/- 5	75	0.001
	12.5	11.23	19 +/- 4	82	0.001
	25	22.46	11 +/- 1	89	0.001

*mean of results +/- standard error of the mean (SEM)
**Student test
***aggregation height in mm mean +/- SEM (n = 5)
n.s. not significant

For the aggregation with collagen, the percentage of inhibition is the difference of the slopes of the curves representing the variation of the optical density as a function of time for the control and the product to be tested divided by the slope of the control multiplied by 100. The results shown in Table II demonstrate again that only the dextro-rotatory isomer is active whereas the salts have comparable activities.

TABLE II

PRODUCT	DOSE mg/Kg P.O	QUANTITY of base administered	SLOPE	% INHIBITION	P**
Controls			4.8 +/- 0.3		
PCR 4099	4.48	3.84	3.6 +/- 0.2	25	0.05
(racemate)	8.97	7.69	2.7 +/- 0.3	44	0.01
	17.9	15.38	1.5 +/- 0.3	69	0.001
SR 25989C	20	15.38	4.3 +/- 0.2	10	n.s
	40	30.76	4.0 +/- 0.2	17	n.s
SR 25990C	1.25	0.96	4.3 +/- 0.3	6	n.s
	2.5	1.92	4.1 +/- 0.2	15	n.s
	5	3.84	2.3 +/- 0.1	52	0.001
	10	7.69	1.7 +/- 0.3	65	0.001
Controls			3.5 +/- 0.1		
SR 25990E	10	3.84	2.1 +/- 0.5	60	0.05
	20	7.69	1.4 +/- 0.4	60	0.01
Controls			3.97 +/- 0.29		
PCR 4099	2.5	2.14	3.13 +/- 0.33	21	n.s
(racemate)	5	4.28	2.94 +/- 0.36	26	0.05
	12.5	10.71	2.19 +/- 0.42	45	0.01
SR 25989A	25	22.46	4.32 +/- 0.29	10	n.s
SR 25990A	2.5	2.25	3.05 +/- 0.19	23	0.05
	5	4.49	1.24 +/- 0.22	69	0.001
	12.5	11.23	0.86 +/- 0.14	78	0.001
	25	22.46	0.74 +/- 0.13	81	0.001

**Student test
n.s. not significant

The antithrombotic activity of these compounds has also been studied in the test of venous thrombosis on a screw thread described by Kumada T. et al. in Thromb. Res 18 p. 189 (1980).

Female rats of the same type as those previously described, in groups of 10 animals, were anesthetized with diethyl ether and their vena cava was isolated after abdominal incision.

A metallic screw thread 21 mm long consisting of a dentist's drill, marketed by Dyna (France) size No. 30, was introduced into the lumen of this vein just below the renal bifurcation descending towards the iliac veins, without damaging the wall; 19 to 20 mm of the length of the screw thread are implanted and the remaining 1 mm protrudes through the closed stomach into the exterior.

The thrombi formed rapidly and five hours later, under pentobarbital anesthesia, the abdomen is reopened and ligatures are placed above and below the screw thread which is withdrawn after longitudinal incision of the vein and the isolated thrombus is weighed.

The results which are presented in Table III show that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer and the racemate.

TABLE III

PRODUCT	DOSE mg/Kg P.O admin.	QUANTITY of base	WEIGHT of thrombi*	VARIATION %	P**
Controls			3.9 +/- 0.3		
PCR 4099	4.48	3.84	2.17 +/- 0.24	44	0.001
(racemate)	8.97	7.69	1.39 +/- 0.19	64	0.001
	17.9	15.38	1.00 +/- 0.19	74	0.001
SR 25989C	40	30.76	4.17 +/- 0.42	-7	n.s
SR 25990C	1.25	0.96	3.11 +/- 0.32	20	n.s
	2.5	1.92	2.29 +/- 0.22	41	0.01
	5	3.84	1.71 +/- 0.24	56	0.01
	10	7.69	1.26 +/- 0.19	67	0.01
	20	15.38	1.20 +/- 0.13	69	0.01

TABLE III-continued

PRODUCT	DOSE mg/Kg P.O admin.	QUANTITY of base	WEIGHT of thrombi*	VARIATION %	P**
Controls			3.78 +/− 0.36		
SR 25990E	10	3.84	1.48 +/− 0.15	60	0.001
	20	7.69	1.16 +/− 0.15	68	0.001

* = weight of thrombi in mg +/− standard error of the mean
P = U test of Kruskal - Wallis

For the toxicological study, the compounds were administered by the oral route in the form of a suspension in the same volume of water made up to 10% (wt/v) with gum arabic to groups of 10 fasted female rats of the Sprague Dawley strain weighing 120 to 135 grams.

The number of dead animals was determined 14 days after the administration of the compound under study. The lethal doses thus determined, expressed in weight of the salt administered, are presented in Table IV; these results show on the one hand that the toxicity of the racemic mixture is similar to that of the levo-rotatory isomer whereas the dextro-rotatory isomer is markedly less toxic, and, on the other hand, that the toxicity depends on the nature of the acid used to form the salt.

TABLE IV

PRODUCTS	D 10	D 50 ( )	D 90	ABSOLUTE LETHAL DOSE
PCR 4099 (racemate)	1318	1615 (1448–1747)	1979	2000
SR 25989 A	1259	1702 (1443–1797)	2299	2000
SR 25990 A	3053	4316 (3569–5705)	6137	5000
SR 25990 C	2257	2591 (2372–2805)	2974	4000
SR 25990 D	2634	4268 (3381–6012)	6914	5000

( ) = confidence interval

The pharmacological study just presented has demonstrated the interesting inhibitory properties towards platelet aggregation of the compound Id and the absence of any activity of its isomer I1.

The medicine of the invention can be made available for oral administration in the form of tablets, sugar-coated tablets, capsules, drops, granules or a syrup. It can also be made available for rectal administration in the form of suppositories or for parenteral administration in the form of an injectable solution.

Each unit dose contains advantageously from 0.001 g to 0.100 g of the derivative of the invention, and the daily doses to be administered may vary from 0.001 g to 0.500 g of active ingredient depending on the age of the patient and the severity of the disorder to be treated. Some pharmaceutical formulations of the medicine of the invention will be given below as non-restrictive examples.

(1) Tablets

Active ingredient: 0.010 g

Excipient: lactose, powdered sugar, rice-starch, alginic acid, magnesium stearate

(2) Sugar-coated tablets

Active ingredient: 0.005 g

Excipient: magnesium stearate, maize starch, gum arabic, shellac, white sugar, glucose, white wax, carnauba wax, paraffin, cochineal.

(3) Capsules

Active ingredient: 0.025 g

Excipient: magnesium stearate, maize starch, lactose.

(4) Injectable solution

Active ingredient: 0.050 g

Isotonic saline q.s.p. 3 ml

(5) Suppositories

Active ingredient: 0.030 g

Semi-synthetic triglycerides q.s.p. 1 suppository.

On account of its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracoporeal blood circuits or the consequence of complications in atheroma.

We claim:

1. Dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer and its pharmaceutically acceptable salts.

2. Hydrochloride of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

4. Hydrobromide of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

5. Taurocholate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

6. Pharmaceutical composition which comprises an effective platelet aggregation inhibiting amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

7. Composition according to claim 6, comprising unit doses containing from 0.001 g to 0.100 g of active ingredient.

* * * * *

140

(4)

OFFICE OF THE CLERK

No. 09-117

IN THE

Supreme Court of the United States

APOTEX, INC. AND APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., AND BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION

Robert L. Baechtold
John D. Murnane
William E. Solander
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, NY 10104-3800
Telephone: (212) 218-2100

Evan R. Chesler
Counsel of Record
Richard J. Stark
David Greenwald
CRAVATH, SWAINE & MOORE LLP
825 Eighth Avenue
New York, NY 10019-7475
Telephone: (212) 474-1000

Rule 29.6 Statement

The parent corporations and/or the publicly held companies that own 10 percent or more of the stock of Respondents are:

Sanofi-Aventis
Bristol-Myers Squibb Company
Total
L'Oreal

Table of Contents

Page

Table of Authorities ii

Statement 1

A. Factual Background 3

B. The Proceedings Below 12

1. The District Court 12

2. The Federal Circuit Appeal 16

3. The Pending Reexamination Proceedings 18

Argument 19

I. The Petition Should Be Denied. 19

A. The Decisions Below Are Not In Conflict With *KSR* 19

B. Enantiomer Patents Do Not Require a Special Obviousness Standard. 26

C. *KSR* Did Not Reject the Principle that "Obvious to Try" Is Generally Not the Standard for Obviousness Under 35 U.S.C. § 103. 27

D. The Petition Raises No Serious Public Policy Issue. 29

Conclusion 31

Table of Authorities

Page(s)

Cases

Abbott Labs. v. Sandoz, Inc.,
544 F.3d 1341 (Fed. Cir. 2008) 29

Anderson's Black Rock, Inc. v. Pavement Salvage Co.,
396 U.S. 57 (1969) 20

Aventis Pharma Deutschland GmbH v. Lupin, Ltd.,
499 F.3d 1293 (Fed. Cir. 2007) 27

Bayer Schering Pharma AG v. Barr Labs., Inc.,
575 F.3d 1341 (Fed. Cir. 2009) 28, 29

Eisai Co. Ltd. v. Dr. Reddy's Labs.,
533 F.3d 1353 (Fed. Cir. 2008) 29

Forest Labs., Inc. v. Ivax Pharms., Inc.,
501 F.3d 1263 (Fed. Cir. 2007) 27

Gen. Elec. Co. v. Jewel Incandescent Lamp Co.,
326 U.S. 242 (1945) 22

Graham v. John Deere Co. of Kan. City,
383 U.S. 1 (1966) ..... passim

In re Adamson,
295 F.2d 952 (C.C.P.A. 1960) 27

Page(s)

In re Kubin,
561 F.3d 1351 (Fed. Cir. 2009) 23, 28

In re May,
574 F.2d 1082 (C.C.P.A. 1978) 25, 26, 27

In re Nolan,
553 F.2d 1261 (C.C.P.A. 1977) 25

In re O'Farrell,
853 F.2d 894 (Fed. Cir. 1988) 28

KSR Int'l Co. v. Teleflex, Inc.,
550 U.S. 398 (2007) ..... passim

Muniauction, Inc v. Thomson Corp.,
532 F.3d 1318 (Fed. Cir. 2008) 28

Mycogen Plant Science v. Monsanto Co.,
243 F.3d 1316 29

Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.,
520 F.3d 1358 (Fed. Cir. 2008) 28

Pfizer v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007) 24, 25

Sakraida v. Ag Pro, Inc.,
425 U.S. 273 (1976) 20

Sanofi-Synthelabo v. Apotex, Inc.,
470 F.3d 1368 (Fed. Cir. 2006) 12

Page(s)

Sanofi-Synthelabo v. Apotex, Inc.,
550 F.3d 1075 (Fed. Cir. 2008), *reh'g denied*, Mar. 26, 2009 16

Sanofi-Synthelabo v. Apotex, Inc.,
488 F. Supp. 2d 317 (S.D.N.Y. 2006) 12

Sanofi-Synthelabo v. Apotex, Inc.,
492 F. Supp. 2d 353 (S.D.N.Y. 2007) 12

Sud-Chemie v. Multisorb Techs.,
554 F.3d 1001 (Fed. Cir. 2009)..... 24

Takeda Chem. Indus. v. Alphapharm Pty., Ltd.,
492 F.3d 1350 (Fed. Cir. 2007)..... 24, 29

United States v. Adams,
383 U.S. 39 (1966) 2, 20

Statutes & Rules

35 U.S.C. § 103.....passim

Other Authorities

Patent Office's Manual of Patent Examining Procedure, Section 2242..... 19

Statement

This case arises out of Petitioners' ("Apotex's") challenge to the validity of Claim 3 of U.S. Patent No. 4,847,265 (the "'265 Patent"), which claims clopidogrel bisulfate, marketed by Respondents in the United States under the brand name "Plavix®." Plavix® is indicated for the prevention of heart attacks and strokes, and is the most widely-used prescription anticlotting agent.

Following well-established law, both the District Court and the Federal Circuit held that, even if it were assumed that Apotex had made out a case of "prima facie obviousness" based on the structural similarity of clopidogrel, the "dextrorotatory enantiomer," to the previously described "racemic" compound, PCR 4099, three properties that even Apotex's experts conceded were unpredictable amply rebutted that prima facie case. Those three properties were:

- the unexpectedly complete concentration of anticlotting activity in clopidogrel; its opposite, "levorotatory" enantiomer had none;

- the unexpectedly complete concentration of PCR 4099's troubling neurotoxicity (*i.e.*, potential to cause seizures) in the inactive, levorotatory enantiomer; the active enantiomer, clopidogrel, had no neurotoxicity; and

- the unexpectedly favorable crystalline properties of the bisulfate salt of clopidogrel — a salt from which the prior art "taught away" — that made clopidogrel bisulfate unusu-

ally favorable for formulation as an orally administered tablet.

These three properties, in addition to being unexpected, lay at the core of the features of this drug that made it not only novel, but a breakthrough, approvable, safe and marketable drug. Contrary to the expectation of experts for both parties, *all* the activity of the prior art racemate resided in clopidogrel, yet that active enantiomer was devoid of the racemate's convulsive potential. This ensured that the compound was safe enough to win FDA approval. And the unusually favorable constellation of properties of the bisulfate salt (*e.g.*, stability, lack of hygroscopicity, high melting point), made this daily-dosed drug commercially marketable.

In wrongly accusing the court below of a "fixation on unexpectedness or unpredictability" that "clashes with this Court's decisions" (Pet. 14), [1] Apotex notably avoids pertinent aspects of this Court's obviousness jurisprudence, *e.g.*, *United States v. Adams*, 383 U.S. 39, 51-52 (1966) (existence of unexpectedly favorable property supports a finding of non-obviousness). Apotex also equally incorrectly argues that the resolution of this case conflicted with the teaching of *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), about when an invention that results from an approach that is "obvious to try" can be obvious under 35 U.S.C. § 103. (*See* Pet. 12-13.) This case did not even graze that teaching because the in-

---

[1] Citations to the Petition are in the form "Pet."; citations to the Petition's appendix are in the form "#a"; citations to the joint appendix submitted in the Federal Circuit are in the form "A#".

ventive approach Sanofi followed was emphatically not "obvious to try," and neither lower court made any such factual finding. Nor could they. This was not a case in which there were "a finite number of identified, predictable solutions" that this Court indicated in *KSR* might support a conclusion that an invention is obvious to try. *See KSR*, 550 U.S. at 421. Moreover, as noted above, the chemical compound claimed here produced results that were not "anticipated," but rather were contrary to the expectations of both sides' experts.

In short, this case is an especially poor vehicle for considering the question Apotex presents or, more generally, the circumstances under which an inventive approach that is "obvious to try" is obvious under § 103.

A. Factual Background[2]

The petition concerns the U.S. patent on clopidogrel bisulfate, marketed in the U.S. by Respondents as Plavix®. Plavix® is an antiplatelet-aggregation drug prescribed to prevent heart attacks and strokes. (A485; A8480-A8481.)

Clopidogrel bisulfate was the successful culmination of a 15-year research program at the French drug company, Sanofi, now known as Sanofi-Aventis. (*See* 4a-12a.) Sanofi began studying a class of compounds called "thienopyridines" in the hope of finding drugs to combat inflammation. (36a.) They

---

[2] The facts concerning the invention of clopidogrel bisulfate are also described in the Federal Circuit's opinion. (4a-12a.)

found none that had that property, but serendipitously discovered that some had the ability to inhibit blood clotting. (36a; A12195:25-A12198:2.) Those compounds might therefore be able to prevent heart attacks and strokes.

After considerable work, Sanofi discovered the drug, "ticlopidine," which had potent anticlotting activity. (36a; A12201:2-12.) Unfortunately, after the drug had been marketed for several years in Europe and the United States, it became apparent that ticlopidine, in rare instances, caused serious and potentially fatal, blood disorders. (37a; A12203:25-12205:3.) Sanofi set out to find a safer alternative to ticlopidine. (37a-44a.)

Over the course of several years, Sanofi made and tested over 600 chiral thienopyridines. (61a; A12241:21-A12243:3.) Most failed either because they were not potent enough or were too toxic for clinical use. Sanofi found, however, that a class of thienopyridines that differed from ticlopidine at a certain position in the molecule were potent anticlotting agents and appeared to be better tolerated than ticlopidine. (A12262:13-21; A12263:19-22; A12264:10-A12265:12.) That invention was disclosed and claimed in U.S. Patent No. 4,529,596 (the "'596 Patent"). (*See* 43a-45a.) The '596 Patent disclosed more than a million compounds. (46a; A12395:5-12; A12538:1-3.)

Unlike ticlopidine, the '596 Patent compounds had what chemists called a "chiral center," which meant they could exist in right-handed or left-handed configurations called "enantiomers." (38a; 46a.) All of the compounds the '596 Patent disclosed

were 50:50 mixtures of those two configurations, which are called "racemic." (38a; 46a; A10201:9-16; A12537:8-10.) Unless chemists employ special procedures that either create only one of the two configurations or separate each from the 50:50 mixture, chemical syntheses produce only the racemic form.

Isolating individual enantiomers was then, and still is now, an unpredictable exercise. (100a; A12545:8-17; A12562:23-A12563:19; A28309.) The evidence was that a chemist must choose from a variety of procedures either to create a single enantiomer or isolate one from a racemic mixture (also known as a "racemate"). (100a-101a.) Which, if any, of those procedures, each of which requires multiple choices of reaction conditions and reagents, would work for any specific compound was unpredictable and likely to require considerable trial and error. (61a; A12562:23-A12563:19.)

Of the 600 chiral compounds Sanofi made, Sanofi had only twice attempted (prior to PCR 4099) to obtain the individual enantiomers of any racemic compound. (A10209:21-25; A12215:22-A12217:1; A12241:21-A12243:3.) Both of those racemic compounds (called "PCR 1033" and "PCR 3549") had anticlotting activity but were too toxic to be therapeutically acceptable. (A11211:25-A11212:6; A12222:7-A122234; A12242:25-A12243:3.) In each case, Sanofi was able to separate the individual enantiomers, but separating the enantiomers did not solve the toxicity problem because each enantiomer retained an unacceptable level of toxicity. (37a-43a; A12277:4-19.) In the case of one of those two racemates, PCR 1033, one enantiomer was more active than the other. (A12222:7-A12223:5.) In the case of the other, PCR

3549, the two were equally active. (A12320:23-A12324:11.) Sanofi regarded each of those enantiomeric separations as failures. (A10199:3-6; A12223:18-24; A12321:6-A12324:11.)

In theory, the maximal increase in activity attainable through the separation of enantiomers of a racemic compound would be a two-fold increase in potency: a result that would be achieved only if, as was rare, one enantiomer (after metabolic processing, if any) possessed all the activity and the other possessed none. (Opinion A41; A12920:9-A12924:3; A17875; A19534-19536 (tbls. 1, 2); A19540 (fig. 11); A12215:22-A12217:1.) In practice, the difference in potency between two enantiomers was more often significantly less stark. (57a-58a; A11196:8-A11200:17; A12838:19-A12839:19; A12919:17-A12923:7; A13148:9-11; A19534-19536 (tbls. 1, 2); A19540 (fig. 11).) With respect to the different pharmacological activity of enantiomers, the prior art offered comprehensive tables showing that although enantiomers often differed in their activity, the nearly universal situation was one in which each enantiomer had some activity. (57a-58a.)

Of the compounds described in the '596 Patent, Sanofi chose to develop one, PCR 4099, as a potential anticlotting medicine. (*See* 53a.) PCR 4099 was a racemic compound. Before undertaking that development, Sanofi did not try to obtain the individual enantiomers, but planned to obtain approval and sell it as a racemate. (53a-56a.) Regulatory standards did not require companies to obtain and test the individual enantiomers of racemic compounds as a condition for approval. (*See* 82a.) Indeed, as of 1980, approximately 80 percent of chiral drugs were sold in

racemic form, and that remains common even today. (A11183:6-13; A11205:8-16; A13814; A17873.) Sanofi invested seven years of effort and spent tens of millions of dollars to develop PCR 4099 as a racemic compound. (80a.)

In addition to the difficulty and unpredictability inherent in obtaining individual enantiomers, and Sanofi's own prior failures to improve the toxicity/activity profiles of PCR 1033 and PCR 3549, Sanofi was aware of another disincentive to undertake that exercise. It knew that the thienopyridines were not active as such, but had to be converted ("metabolized") to a different chemical structure in the body before they were effective. But it did not know what that structural change was. (60a; A10214:13-A10215:8; A11209:11-A11210:3.) Therefore, it was possible that obtaining the individual enantiomers (in addition to failing to yield any improvement over the racemate, as had occurred with PCR 1033 and PCR 3549) might be futile if the body's metabolic processes removed the chiral center or caused the enantiomer to revert back into the racemic form.[3] (A11209:12-19.) In fact, the chemical structure of PCR 4099 was such that it would be especially susceptible to "racemization." (*See* A12453:16-A12454:16.)

---

[3] Ironically, thalidomide — the example Apotex cited of an inactive enantiomer having the undesirable toxicity — is also an example of that futility. Thalidomide, the nontoxic enantiomer, is converted by the body into the toxic one. Therefore, thalidomide, which has several approved medical uses, is sold in racemic form. (A10235:21-A10237:13; A11204:18-A11205:7.)

Nevertheless, Sanofi decided to try to obtain the individual enantiomers of PCR 4099, to see if that might produce any improvement in the safety profile. (55a-56a.) There was at best a hope, but not an expectation, that might be the result. (79a; A12275:13-25.) While the Sanofi chemists knew that the properties of the two enantiomers might be different, there was no way to predict if they would be different, at least to any meaningful degree. (58a-59a; A10235:14-A10237:23; A13812.)

Sanofi chemist, Alain Badorc, set out to obtain the enantiomers of PCR 4099. (55a-56a; A10209:6-11; A10211:10-16; A12274:25-A12275:12; A13214:4-8.) Initially, he tried techniques that had worked for PCR 3549, but those techniques failed. (65a-66a; A12453:6-15; A12454:10-16; A12459:24-A12461:15; A28281-A28284; A12121:20-24; A12122:12-14; A25895-A25896; A25937-A25938.) As feared, the products "racemized." (*See id.*) Finally, after five months of trial and error, and by using a technique called diastereomeric salt formation, with a combination of solvents, reactants and conditions that were not taught by the prior art, Badorc succeeded in obtaining the two enantiomers of PCR 4099. (67a-69a; A12466:5-A12474:20; A25904; A26699; A26743.)

Those tests gave a striking result: the dextrorotatory enantiomer (clopidogrel) was active, while the levorotatory enantiomer was completely inactive. (75a; A10213:19-A10214:7; A12283:4-11; A13150:3-6; A13151:2-A13153:10; A13254; A13888-A13890; A14919; A14923; A14924; A18412; A8907; A8923.) The enantiomers of PCR 4099 thus exhibited the rare characteristic of "absolute stereoselectivity."

(58a; 75a; A19534-A19536 (tbls. 1, 2); A19540 (fig. 11); A12923:8-A12924:3; A17875.)

When toxicological tests were performed, an even more surprising result was obtained. In a comparative acute toxicity study of PCR 4099 and its enantiomers, convulsions were observed in animals receiving PCR 4099 or the levorotatory enantiomer, but no convulsions were observed in animals receiving clopidogrel. (A12289:11-19; A13001:8-24; A27250-A27251; A27554-A27555.) This was very surprising because, if anything, the prior art had suggested that activity and toxicity might correlate with one another. (23a ("The experts also agreed that activity and toxicity were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity.").) The complete lack of correlation seen here flew in the face of any ordinarily skilled person's expectation.

Based upon the surprising test results for clopidogrel, in April 1987, Sanofi made the decision to abandon further clinical development of PCR 4099. (A10218:15-20; A26000-A26001.) From its synthesis in 1980 up until the decision to discontinue its development, Sanofi had spent tens of millions of dollars developing PCR 4099. The decision to discontinue its development set back Sanofi's effort to market a successor to ticlopidine by four years. (80A; A10220:4-6.)

Another surprise occurred as Sanofi moved forward with the development of clopidogrel. To have a medicine in a form that can be used in practice, it must be solid, stable and not absorb water from the

atmosphere (*i.e.*, it must be "non-hygroscopic"). (74a.) For PCR 4099, which was the mixture of clopidogrel with an equal amount of its opposite enantiomer, the hydrochloride salt met all those requirements. (11a.) However, it was not satisfactory for the isolated clopidogrel enantiomer, because it was hygroscopic and unstable. (A11962:12-18; A12477:12-A12478:11.) Accordingly, to market clopidogrel as a tablet, it would be important to discover a more suitable salt. (69a; A12477:12-A12478:11; A25868.)

Pharmaceutical salt development — the process of combining basic or acidic drugs with acids or bases to form (hopefully) crystalline solids — is a highly unpredictable area of medicinal chemistry. (71a-72a.) Whether a crystalline material will form, and the properties that material will have, are unpredictable. (A11167:19-A11168:23; A11725:20-A11726:1; A11946:12-A11948:1; A12272:13-20; A12569:13-A12571:16; A12746:20-A12747:14.) Scientific articles noted the unpredictable nature of pharmaceutical salt selection. (A17448; A27649; A20708.)

Lacking any guidance from the prior art or its own prior work on thienopyridines, Sanofi searched for a suitable salt through a process of trial and error. Between approximately May and June 1987, more than a year after the successful synthesis of clopidogrel, Badorc and others tested at least 21 different acids in combination with clopidogrel, in search of a salt with the desired properties. (A11974:12-A11975:3; A12397:21-A12398:1; A12477:20-A12480:22; A25868-A25872; A26600; A26603-A26608; A26610-A26615; A26631; A26680; A26681-A26686; A26687-A26692; A26694; A26704;

A26748.) After the results of all the screens were obtained, only the bisulfate salt had the desired combination of properties: high melting point and long-term stability, non-hygroscopicity, and solubility. (A11981:14-18; A12479:7-24; A12773:3-9.)

This result was surprising, and not just because of the inherent unpredictability of salt selection. If anything, the prior art would have taught *away* from using sulfuric acid (the acid used to form the bisulfate salt) to form a salt of clopidogrel. A 1986 article teaches the use of *organic* acids as a substitute for hydrochloric acid when a hydrochloride salt is hygroscopic, rather than strong *mineral* acids, such as sulfuric acid. (*See* A20717-A20720.) Thus, the bisulfate salt would be expected to be more hygroscopic than the hydrochloride. (74a-75a; A12779:12-A12787:10; A27930-A27932; A20717-A20720, (fig. 5), (tbl. 3).) The opposite, however, proved true. Further, the bisulfate anion (unlike other salt anions) had the potential to racemize an enantiomerically pure ester such as clopidogrel, thus recreating the toxicity problems that the separation had eliminated. (74a-75a; A12585:16-20; A12594:18-A12596:5; A28317.) Yet the bisulfate salt of clopidogrel is very stable. (A11981:14-18; A12479:7-24; A12773:3-9.)

In February 1988, Sanofi filed an application for a U.S. patent on clopidogrel and certain of its salts, including the bisulfate (the "'265 Application"). (A15104; A15108.) The examiner of the '265 Application had also served as the examiner of the '596 Patent, and he cited and considered the latter in the examination that resulted in the patent in suit. (85a; A15104; A15107; A15160; A15163; A14909.) On July 11, 1989, the '265 Patent issued.

B. The Proceedings Below

1. The District Court

The action below was commenced by Respondents in 2002 shortly after Apotex filed an abbreviated new drug application ("ANDA") to market clopidogrel bisulfate. (A486.) Apotex admitted infringement of Claim 3 of the '265 Patent, but asserted anticipation, obviousness, obviousness-type double-patenting, and inequitable conduct as defenses. (A322-A326; A486.)

On August 8, 2006, six months after the FDA approved its ANDA, and while suit was pending, Apotex began selling clopidogrel bisulfate. Very promptly thereafter, Respondents moved for a preliminary injunction. On August 31, 2006, the District Court granted Respondents' motion, *Sanofi-Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317 (S.D.N.Y. 2006), and the Federal Circuit affirmed. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006).

A four-week trial occurred during January and February 2007 before Judge Sidney H. Stein. In June 2007, after receiving post-trial briefing from the parties concerning the impact of this Court's intervening, April 30, 2007 decision in *KSR*, the District Court held the patent was not invalid and not unenforceable, and entered a judgment permanently enjoining further infringement. *Sanofi-Synthelabo v. Apotex, Inc.*, 492 F. Supp. 2d 353 (S.D.N.Y. 2007). In a detailed opinion, the District Court found, among other things, that, with respect to the properties of separated enantiomers generally:

> Where there is variation, the extent of that variation is not predictable and can be weak, moderate, or strong — a view confirmed by experts from both parties and credited by this Court . . . . Dr. Robert Snyder, an expert for Apotex, testified that without separating and testing the enantiomers of a particular racemate, a [POSA] could not know what the degree of difference — if any — between the properties of the enantiomers of a racemic compound would be . . . . The prior art, in fact, suggested that 'weak' stereoselectivity — i.e., a difference in activity of 10-fold or less between two stereoisomers — was fairly common and that strong stereoselectivity — i.e., a difference in activity of 100-fold or more between stereoisomers — was less prevalent. . . . Experts from both parties agreed that even today, no scientific principles afford a basis for predicting to what degree, if any, a pair of stereoisomers will exhibit different levels of therapeutic activity and different levels of toxicity.

(58a.)

For that reason, the extreme result that obtained from the separation of the enantiomers here — the complete segregation of activity to only one of the two enantiomers, *i.e.*, "absolute stereoselectivity" — was "uncommon." (58a.) Even more striking and unexpected was that the enantiomer having all the activity, clopidogrel, possessed *none* of the racemate's neurotoxicity; the latter, undesirable property resided solely within the inactive enantiomer. (79a.)

"[A]s experts from both parties agree — it was not possible to predict whether either enantiomer would be . . . more or less toxic — than the other." (61a.)

The District Court further appreciated the complexity of pharmaceutical salt development:

> Formation of a crystalline salt is important for an orally administered drug such as clopidogrel, and the salt form of a drug can affect a drug's pharmacological properties... However, the prior art teaches — and both parties' experts agreed and the Court finds — that whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable.

(71a-72a.)

On the basis of these findings, the District Court found further that clopidogrel bisulfate possessed not fewer than three unexpected properties compared to the closest prior art, PCR 4099 and its hydrochloride salt. Specifically, the District Court concluded it was unexpected that (i) all the activity of PCR 4099 would reside in clopidogrel while the levo-rotatory enantiomer would possess none, (ii) the inactive enantiomer would possess all the racemate's neurotoxicity, and clopidogrel none, and (iii) the bisulfate salt would possess a "highly desirable combination of properties," rendering it most suitable for commercial use. (112a-113a.)

In addition to the prior art, which offered no basis for expecting any of the foregoing, the District Court found particularly relevant the actions of Sanofi's own scientists, whom it found to be "skilled":

> Sanofi spent four years and 'tens of millions of dollars' developing and extensively testing the racemate PCR 4099 before deciding to try separating the enantiomers of the racemic mixture . . . . Apotex has not made a persuasive case . . . as to why the skilled chemists at Sanofi . . . would have acted — as Apotex contends — so contrary to the hypothetical [POSA].

(108a.) The District Court also noted that, at conferences, Sanofi representatives made poster presentations and distributed abstracts concerning PCR 4099. It further found that "a person of ordinary skill in the art would not have drawn any inference from those materials concerning the stereoselectivity of platelet inhibition by the enantiomers of PCR 4099" but to the contrary, "would have concluded the PCR 4099 was under development as a promising racemic drug with several positive qualities and no significant reported negative qualities." (55a.)

With respect to Apotex's argument that the decision to separate the enantiomers of PCR 4099 had been influenced by regulatory requirements, the District Court credited the "extensive trial testimony and documentary evidence" showing that Sanofi was not influenced by "any nascent regulatory trend mandating the investigation of enantiomers." (81a-82a.) Applying the factors set forth in *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1 (1966), the

District Court held that Apotex had failed to meet its burden of establishing obviousness by clear and convincing evidence. Although the District Court assumed, "[f]or purposes of analysis . . . that Apotex has made a prima facie case of obviousness" (106a), the District Court concluded that each of the unexpected properties identified above rebutted that prima facie case (107a-111a). Far from ignoring Apotex's "obvious to try" argument, the District Court directly met it, saying: "Whether or not it may have been 'obvious to try' separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious." (112a.)

2. The Federal Circuit Appeal

The Federal Circuit affirmed the decision of the district court. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008), *reh'g denied*, Mar. 26, 2009. Noting that "the determination of obviousness is dependent on the facts of each case" (citing *Graham*, 383 U.S. 1) (28a), the Federal Circuit upheld the factual findings of the District Court. (30a.) It affirmed the District Court's finding that "a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an enantiomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity." (30a.) In the latter regard, the court noted the concession of Apotex's expert, who, "when asked whether one could predict

in advance the therapeutic and toxic properties of the enantiomers, stated: 'No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anybody presuming anything else.'" (23a.)

The Federal Circuit also addressed the *KSR* consideration whether there were "a finite number of predictable solutions" that led to an "anticipated success," *KSR*, 550 U.S. at 421, by affirming the finding "that th[e] separation [of PCR 4099] was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable." (25a.) "[N]either the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration." (25a-26a.) And with respect to the unexpectedly favorable properties of the bisulfate salt, the Federal Circuit also affirmed the District Court's findings. "Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt . . . . The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable." (26a-27a.)

The Federal Circuit criticized Apotex's arguments for relying on the hindsight knowledge that clopidogrel bisulfate was a useful drug. (26a.) *See Graham*, 383 U.S. at 36 (cautioning against hindsight whereby the teachings of the invention are read

into the prior art); *see also KSR*, 550 U.S. at 421 (recognizing "hindsight bias" and "*ex post* reasoning" as inappropriate in determination of obviousness). "Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation." (26a.) The Federal Circuit concluded its opinion with a discussion of the consistency of the District Court's reasoning with the patent law principles reiterated in *KSR* (29a-30a), and affirmed the decision of the District Court.

Apotex's petition for rehearing and rehearing *en banc* before the Federal Circuit was denied without dissent.

3. The Pending Reexamination Proceedings

Six months after the Federal Circuit decision rejecting Apotex's challenges, Apotex submitted to the USPTO a request to conduct an *ex parte* reexamination of the '265 Patent. That request relied solely on patents, publications and arguments on which Apotex had unsuccessfully relied in the litigation (and citing as the principal reference the '596 Patent, which was previously cited to and considered by the Examiner in granting the '265 Patent and its Canadian counterpart). On August 17, 2009, the USPTO granted the request, on the ground that there was a substantial new question of patentability, *i.e.*, Apotex submitted to the USPTO some additional prior art that had not been considered in the original prosecu-

tion (but which had been among the exhibits Apotex listed during the trial proceedings below).[4]

Argument

I. The Petition Should Be Denied.

A. The Decisions Below Are Not In Conflict With *KSR*.

As in the proceedings below, Apotex suggests that this Court's decision in *KSR* mandates a finding of Section 103 obviousness for any invention that was "obvious to try," even if the results that were achieved by the invention were not predictable. (Pet. 2, 11.) That position is rejected by *KSR* itself. The relevant portion of *KSR* discussing the circumstances under which approaches that are "obvious to try" may be obvious, expressly contemplates solutions that are "predictable" and that have "anticipated success." 550 U.S. at 421. Indeed, *KSR*'s review of pre- and post-*Graham* decisions reconfirmed that predictability was an essential attribute of any solution that could reasonably be described as "obvious."

For example, *KSR* began its analysis by affirming the principle that "[t]he combination of familiar

---

[4] As explained in the Patent Office's Manual of Patent Examining Procedure, Section 2242: "[i]t is not necessary that a 'prima facie' case of unpatentability exist as to the claim for 'a substantial new question of patentability' to be present as to the claim." USPTO filing data published through June 30, 2009 indicate that, since the introduction of the ex parte reexamination procedure in 1981, such ex parte requests have been granted 92% of the time. *See* http://www.uspto.gov/web/ patents/documents/ex_parte.pdf (accessed September 24, 2009).

elements according to known methods is likely to be obvious when it does no more than yield *predictable* results." 550 U.S. at 416 (emphasis added). It then compared the outcome in *Adams* (where the invention was found nonobvious) to the outcome in *KSR* because "[t]he fact that the elements [in *Adams*] worked together in an *unexpected* and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art." 550 U.S. at 416 (emphasis added).

By contrast, the inventions in *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976) (which *KSR* also discussed, 550 U.S. at 416-17), were found obvious because the component parts functioned just as they were expected to function, *Anderson's-Black Rock*, 396 U.S. at 60-62, and the combination of elements "yields no more than one would expect from such an arrangement," *Sakraida*, 425 U.S. at 282. As *KSR* summarized: "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 550 U.S. at 417.

Contrary to Apotex's assertions, the two courts below gave appropriate weight to *KSR* and its rationale. The Federal Circuit directly addressed *KSR* by name and concluded that the District Court's fact findings and conclusions were fully consistent with it. (29a-30a.) And although the District Court did not mention *KSR* by name, it received post-trial briefs directed specifically to that case, and assumed *arguendo* that Apotex had made out a *prima facie* case of obviousness (which is the only benefit Apotex

could have obtained from a finding that clopidogrel was "obvious to try"):

> Whether or not it may have been "obvious to try" separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious.

(112a.) In fact, because routes to obtaining individual enantiomers required multiple choices, much trial and error, and no assurance of success, the case here does not even reach *KSR*'s threshold of "a finite number of identified, predictable solutions." 550 U.S. at 421. Nor was the outcome an "anticipated success." *Id.* As Apotex's expert, when asked whether one could predict in advance the therapeutic and toxic properties of the enantiomers, stated: "No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anyone presuming anything else." (23a.)

For those and other reasons, it was hardly "obvious to try" to separate the enantiomers of the racemate to obtain a significantly more potent compound. Because the prior art showed that the activities of enantiomers generally differed to only a moderate degree, the far more promising chemical development strategy was to transform racemic compounds into other, distinct racemic compounds, a strategy that would often generate far more striking,

several-fold differences in activity. (A12215:22-A12217:1.) And if the goal was, as here, to eliminate the racemate's toxicity, nothing in the prior art suggested that enantiomeric separation would accomplish that; indeed, Sanofi's own experience with two prior racemic thienopyridines suggested it would not. (61a; A10214:13-A10215:8; A10199:3-6; A12223:18-24; A12321:6-A12324:11; A12638:17-A12640:9.) Further militating against enantiomeric separation was the circumstance that separating enantiomers often — as here — involved difficult chemistry, in which the prior art offered little guidance, and there was no assurance that any of the many techniques organic chemists could use would work. (A11739:22-A11740:6; A11743:15-A11744:4; A24459.) This was, accordingly, not a case in which "the prior art discloses the method of making an article having the characteristics of the patented product." *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 248 (1945). And even if a technique did work, the possibility that metabolic processes would convert enantiomerically separated compounds back into racemates (as happens with thalidomide (A10235:21-A10237:12; A11204:18-A11205:7)), made the possibility of achieving elimination of toxicity through enantiomeric separation slimmer still. (A10235:14-A10237:13; A12277:4-A12281:21.) For this reason, the Federal Circuit correctly observed that "this case does not concern a combination of familiar elements as in the *KSR* mechanical device." (30a.) It was far more like the throwing of "metaphorical darts at a board filled with combinatorial prior art possibilities," in which the Federal Circuit has held that it remains improper to equate "obvious to try" with

Section 103 obviousness. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Underscoring the nonobviousness of the decision to try to separate enantiomers, was that Sanofi, an experienced, established pharmaceutical company, rarely did it. The evidence showed that during the clopidogrel development process, Sanofi synthesized 600 racemic compounds, but tried to separate the enantiomers of only three. (61a.) And Sanofi dedicated years and millions of dollars to the development of clopidogrel's racemate, only later to try to isolate the enantiomers. (80a-81a.) That investment and approach would not have made sense if it had been in fact "obvious to try" to separate enantiomers from the outset.

The mischaracterization of this case as one in which there were a "finite number of identified, predictable solutions" is also underscored by the findings that the properties of bisulfate salt were not predictable. The eventual discovery that, among all of the possibilities, only the bisulfate salt had the requisite stability and lack of hygroscopicity was taught away from by the knowledge in the art. According to the prior art, hygroscopicity, the chief defect in the hydrochloride salt of clopidogrel, could be remedied by using an *organic* acid to form the salt (not an inorganic acid, like sulfuric acid, which forms the bisulfate). (74a-75a; A12779:12-A12787:10; A27930-A27932; A20717-A20720, (fig. 5), (tbl. 3).) And sulfuric acid, a strong, inorganic acid, posed the risk of racemizing the clopidogrel enantiomer, thus re-generating the risk of neurotoxicity problems that separation had unexpectedly solved. (74a.) It was not obvious that trying any acid offered "anticipated

success," *KSR*, 550 U.S. at 421, of yielding a favorable salt.

This was not a case like *Pfizer v. Apotex*, where the problem to be solved, the elimination of the potential for "Michael addition" reactions that produced impurities, could be solved by using one of only a few acids whose chemical structure rendered it predictably (according to standard organic chemistry textbooks) invulnerable to that type of reaction. 480 F.3d 1348, 1362 (Fed. Cir. 2007). *See also Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359-60 (Fed. Cir. 2007) (discussing *Pfizer*; "other publications [ ] disclosed the chemical characteristics of the besylate salt."). The problem here was to obtain a crystalline salt with favorable properties, a problem on which the prior art provided — and still provides — no guidance other than the trial and error approach Sanofi followed. *Cf.* 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made.").

Mindful that this was a case in which there was an abundance of unpredictable outcomes, Apotex sets up the strawman that the Federal Circuit finds an invention nonobvious if there is *any* degree of unpredictability. To that end, Apotex unfairly characterizes the governing standard as inquiring whether there are "at least some unpredictable properties" or whether "certain aspects of the art are inherently unpredictable" or "not-fully-predictable." (Pet. 11, 12, 17.) But the Federal Circuit and its predecessor court have consistently held that, while unexpected and unpredictable results are relevant to the determination of obviousness, they are not automatically conclusive. *See, e.g., Sud-Chemie, Inc. v. Multisorb*

Techs., Inc., 554 F.3d 1001, 1009 (Fed. Cir. 2009) ("[E]vidence of unexpected results . . . will not necessarily overcome a strong prima facie showing of obviousness."). Rather, they are to be evaluated both for their significance and their weight. *See Pfizer*, 480 F.3d at 1369-72; *In re May*, 574 F.2d 1082, 1095 (C.C.P.A. 1978) ("[A]ppellants here have established a substantial record of unpredictability vis-à-vis a highly significant combination of properties."); *In re Nolan*, 553 F.2d 1261, 1267 (C.C.P.A. 1977) (properties of higher luminous efficiency and lower peak discharge current, though unexpected, did not rebut prima facie case of obviousness).

In re May is especially on point. As here, it involved the patentability of an enantiomer when its racemate was known in the art. As here, the unexpected properties were the separation of the desired activity (analgesia) from the undesirable adverse effect (physical dependence). *May*, 574 F.2d at 1084, 1086. The court explained:

> Since the record reflects both an expected beneficial result, viz., potent analgesia, and an unexpected beneficial result, viz., non-addictive, potent analgesia, it is necessary to determine the weight to be accorded each prior to making the ultimate determination on the issue of obviousness.

Id. at 1092. Accordingly, the court found the balance supported a finding of nonobviousness because of both the degree of unpredictability and the significance of the unexpected results. *Id.* at 1093.

Apotex unfairly characterizes the Federal Circuit's decision here when it asserts: "In hanging patentability on this 'known unknown,' the Federal Circuit essentially said that any element of unpredictability or unexpectedness in an experiment suffices to patent the result." (Pet. 14.) Instead, and consonantly with *May* and other cases, the Federal Circuit found that the properties of clopidogrel bisulfate were both unexpected and significant: "[A] person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity." (30a.)

B. Enantiomer Patents Do Not Require a Special Obviousness Standard.

Apotex also argues that this case is especially certworthy because it involves the patentability of an enantiomer over a previously known racemate. (Pet. 24.) While, to be sure, the Federal Circuit has assessed the validity of a number of patents on separated enantiomers, the analytical approach it has followed is not unique to this corner of pharmaceutical science. Rather, it has been consistent with the approach followed for any other chemical invention, indeed, for any invention of any nature. The Court looks to whether it was routine or difficult to obtain the claimed enantiomer, and whether the properties of the isolated enantiomer were predictable or unexpected.

Thus, patentability has been sustained in cases where, as here, the facts showed that obtaining the enantiomer involved considerable difficulty and/or

the enantiomer, when obtained, displayed properties that were significant and unexpected versus its racemate. *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1269 (Fed. Cir. 2007); *May*, 574 F.2d at 1092-93. Conversely, when the enantiomer was obtained by following established chemistry and its properties were predictable from prior experience with closely-related compounds, the Federal Circuit has not hesitated to find the resulting claim obvious. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) (the patented stereoisomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers."); *In re Adamson*, 275 F.2d 952, 955 (C.C.P.A. 1960). There is, therefore, no intracircuit conflict in the legal analysis applied by the panels in those areas; merely a difference in the factual predicates on which the decisions turned.

C. *KSR* Did Not Reject the Principle that "Obvious to Try" Is Generally Not the Standard for Obviousness Under 35 U.S.C. § 103.

Even if any court had made a finding that the approach here had been obvious to try — and none did — that would not make this case appropriate for this Court's review. On the circumstances under which a solution that is "obvious to try" may be obvious under 35 U.S.C. § 103, the Federal Circuit has faithfully and correctly applied this Court's teaching in *KSR*, and, here too, as in the specific context of enantiomer patent cases, there is no intracircuit split requiring this Court's attention. Apotex's cynical assertion that case outcomes "depend in large part on

who the panelists are" (Pet. 20) and its rhetorical, unsubstantiated allusion to "entrenched confusion" in the Circuit (*id.* at 11) do not withstand a methodical review of the post-*KSR* caselaw.

Heeding *KSR*, the Federal Circuit has struck down some patent claims when the solution they cover would have been obvious to try, in the sense that it combined known elements having known, predictable outcomes/properties. That was the case in *Kubin*, where the claim covered isolation of a polynucleotide coding a specific protein using known biotechnological techniques. *Kubin*, 561 F.3d at 1361. It was also true in *Muniauction, Inc v. Thomson Corp.*, 532 F.3d 1318, 1326-27 (Fed. Cir. 2008), where the claim covered a system for holding internet auctions of municipal bonds and where the prior art disclosed systems for holding internet auctions of other goods. And last month, the Federal Circuit upheld a finding that a claim to the formulation of a known contraceptive drug as a non-enterically coated pill was unpatentable because it would have been obvious to try to formulate the drug as such an ordinary pill, notwithstanding the potential for the drug in the pill, if not enterically coated, to degrade ("isomerize") in the stomach. *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009).

But, in keeping with the general principle, unaltered by *KSR*, that "obvious to try" does not mandate a finding of Section 103 obviousness in areas where the possibilities are numerous not "small" or "easily traversed," *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) — and the results not predictable, *In re O'Farrell*, 853

F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit (as Apotex acknowledges (Pet. 19-20)) has upheld claims against challenges that their inventions were merely "obvious to try." *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008) ("[O]bviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in KSR . . . ."); *Takeda*, 492 F.3d at 1364 (Fed. Cir. 2007) (upholding claim on diabetes drug). It is no accident that these latter, post-*KSR* cases have been drug patent cases. The interaction of chemical compounds with living cells is among the more unpredictable areas of science. *See, e.g., Mycogen Plant Science v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001) (characterizing chemistry and biology as "unpredictable arts"). *See generally Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

D. The Petition Raises No Serious Public Policy Issue.

Finally, and despite Apotex's rhetoric, this is not a petition that raises a serious public policy issue. The '265 Patent is not a patent of the "evergreening" or "lifecycle extension" variety, *cf., e.g., Bayer*, 575 F.3d at 1343-45, one that extends the intellectual property protection of a compound that is already patented, developed, and on the market. Rather, the '265 Patent was a patent on a new, breakthrough drug compound that took years and millions of dol-

lars to develop. Although the predecessor compound, the racemate, entered development and was itself the object of years and millions of dollars in development costs, it never reached the market; Sanofi discontinued its development in 1987 — *before* applying for the patent-in-suit — because of its troubling neurotoxicity. (80a-81a.) The invention that the '265 Patent claims, exemplifies the highly technical, resource-intensive innovation the patent laws and the Hatch-Waxman Act were intended to encourage; innovation that resulted in the development of the world's second most widely prescribed drug (after Lipitor), and which has saved thousands, if not millions of lives. As noted, the life/pharmaceutical sciences are the antithesis of the mechanical arts; unpredictability here is the rule, not the exception. It is alarmist hyperbole when Apotex predicts that, under the Federal Circuit's decision, "[i]f any degree of unpredictability or unexpectedness sufficed to impart patentability, then virtually every new substance could be removed from the public domain for at least 20 years," because "it will never be possible to predict all of the properties of a new substance." (Pet. 23-24.) As explained above, the Federal Circuit has made plain that, for unexpected results to tip the balance in favor of nonobviousness, they must be significant and evaluated in the context of the entirety of the invention: its expected as well as its unexpected properties. If the substance is truly new — as clopidogrel bisulfate was — and if it produces results that are both unexpected and significant, as clopidogrel bisulfate does, it is entirely consistent with the goals of the patent system to grant to the scientists who create it a statutory right to exclude for a limited term.

Conclusion

For the foregoing reasons, the Petition should be denied.

Respectfully submitted,

Evan R. Chesler
Counsel of Record

Robert L. Baechtold
John D. Murnane
William E. Solander
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, NY 10104-3800
Telephone: (212) 218-2100

Richard J. Stark
David Greenwald
CRAVATH, SWAINE & MOORE LLP
825 Eighth Avenue
New York, NY 10019-7475
Telephone: (212) 474-1000

September 2009

142

(5)

No. 09-117

Supreme Court, U.S.
FILED
OCT 13 2009
OFFICE OF THE CLERK

In the Supreme Court of the United States

APOTEX, INC. and APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF FOR PETITIONERS

ROBERT B. BREISBLATT
Katten Muchin Rosenman LLP
525 W. Monroe Street
Chicago, IL 60661
(312) 902-5200

ROBERT S. SILVER
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street
11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of record
DANIEL R. WALFISH
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W.
Suite 411
Washington, D.C. 20006
(202) 775-4500

SHASHANK UPADHYE
Apotex, Inc.
150 Signet Drive
Toronto, ON M9L 1T9
Canada
(416) 401-7701

RULE 29.6 STATEMENT

Petitioners hereby incorporate by reference the statement pursuant to Rule 29.6 included in the petition for a writ of certiorari.

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES iii

I. Respondents Defend the Erroneous View of the Courts Below That Any Element of Unpredictability Is Sufficient To Confer Patentability Even If an Approach Was "Obvious To Try" 2

II. The Federal Circuit Is Intractably Inconsistent 6

III. The Petition Raises A Public Policy Issue of Profound Importance 8

CONCLUSION 11

ADDENDUM:
Federal Court of Australia Decision

TABLE OF AUTHORITIES

Page(s)

Cases

Abbott Labs. v. *Sandoz, Inc.*,
544 F.3d 1341 (2008) 7

Alza Corp. v. *Mylan Labs., Inc.*,
464 F.3d 1286 (2006) 7

Anderson's-Black Rock, Inc. v. *Pavement Salvage Co.*,
396 U.S. 57 (1969) 4

Ansonia Brass & Copper Co. v. *Elec. Supply Co.*,
144 U.S. 11 (1892) 3

Aventis Pharma Deutschland GmbH v. *Lupin, Ltd.*,
499 F.3d 1293 (2007) 7

Bayer Schering Pharma AG v. *Barr Labs., Inc.*,
575 F.3d 1341 (2009) 7

Compton v. *Metal Prods., Inc.*,
453 F.2d 38 (4th Cir. 1971) 3

eBay Inc. v. *MercExchange L.L.C.*,
547 U.S. 388 (2006) 1

Forest Labs., Inc. v. *Ivax Pharms., Inc.*,
501 F.3d 1263 (2007) 7

Graham v. *John Deere Co.*,
383 U.S. 1 (1966) 9

TABLE OF AUTHORITIES – cont'd

Page(s)

In re Kubin,
561 F.3d 1351 (2009) 7

KSR International Co. v. *Teleflex Inc.*,
550 U.S. 398 (2007) 1, 4, 10, 11

Muniauction, Inc. v. *Thomson Corp.*,
532 F.3d 1318 (2008) 7

Ortho-McNeil Pharm., Inc. v. *Mylan Labs., Inc.*,
520 F.3d 1358 (2008) 7

Pfizer, Inc. v. *Apotex, Inc.*,
480 F.3d 1348, reh'g denied,
488 F.3d 1377 (2007) 7

Procter & Gamble Co. v. *Teva Pharms. USA, Inc.*,
566 F.3d 989 (2009) 7

Sakraida v. *Ag Pro, Inc.*,
425 U.S. 273 (1976) 4

Süd-Chemie, Inc. v. *Multisorb Techs., Inc.*,
554 F.3d 1001 (2009) 7

Takeda Chem. Indus., Ltd. v. *Alphapharm Pty., Ltd.*,
492 F.3d 1350 (2007) 7

United States v. *Adams*,
383 U.S. 39 (1966) 4, 6

TABLE OF AUTHORITIES – cont'd

Page(s)

Univ. of Ill. Found. v. *Winegard Co.*,
402 F.2d 125 (8th Cir. 1968) 3

Statutes

35 U.S.C. § 103..... 9, 10

REPLY BRIEF FOR PETITIONERS

In making so much of the supposedly unpredictable aspects of the chemistry at issue, respondents ("Sanofi") advance in this Court the very legal proposition that petitioners ("Apotex") contend is erroneous and warrants further review. Ultimately respondents fail to grapple with petitioners' basic point: An obsessive focus on *outcomes* rather than the *obviousness of the path followed to reach a result* is starkly inconsistent with the approaches of the U.S. Patent and Trademark Office and other courts of appeals in an earlier era; contrary to sound patent policy; and in conflict with a century of this Court's case law culminating in *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007).

Respondents' lengthy brief seems concerned more than anything with calling attention to the sweat of Sanofi's brow. That sweat, however, is legally immaterial. It was already rewarded, moreover, with a valid earlier patent against which the later one at issue must be judged. The petition raises a recurring issue of profound importance, and it should be granted so this Court can clarify that *KSR*'s lessons apply with no less force in an "unpredictable art."[1]

---

[1] Respondents point out that the PTO has agreed to conduct a reexamination proceeding for the '265 patent. BIO 18. In the past this Court has been entirely untroubled by the pendency of such a proceeding. See *eBay Inc.* v. *MercExchange L.L.C.*, 547 U.S. 388, 391 n.1 (2006). In this case, even if the PTO were to invalidate the '265 patent, a final decision to that effect would not issue for many years.

I. Respondents Defend the Erroneous View of the Courts Below That Any Element of Unpredictability Is Sufficient To Confer Patentability Even If an Approach Was "Obvious To Try."

A. Respondents halfheartedly say that Apotex is "unfair[]" to characterize the Federal Circuit's decision as saying that any aspect of unpredictability in an experiment is sufficient to patent the result. Br. in Opp. ("BIO") 26. But the district court clearly believed that "evidence of the fact that *any* property of clopidogrel bisulfate is unexpected . . . rebuts the presumption that clopidogrel bisulfate is obvious," Pet. App. 107a (emphasis added), and respondents defend the court's "conclu[sion] that *each*" one of the compound's supposedly unexpected properties "rebutted that prima facie case," BIO 16 (emphasis added).

The Federal Circuit obviously agreed. It is respondents who repeatedly call attention (BIO 16, 20, 26) to its justification for affirming: "[A] person of ordinary skill would not have had the *expectation* that separating the enantiomers would be *likely* to produce an isomer having [i] absolute stereoselectivity as to *both* [ii] the favorable antiplatelet activity *and* [iii] the unfavorable neurotoxicity." Pet App. 30a (emphasis and bracketed numbers added). In other words, a person of ordinary skill would not have bet all his chips on the precise eventual outcome, even though it was (as Sanofi concedes, BIO 6) within the known range of possible outcomes, see Pet. 4, and (as Sanofi does not really dispute, see BIO 8) there were good, *objective* reasons why someone would want to separate the enantiomers of PCR4099. See Pet. 16; Br. of *Amici Curiae* AARP et

al. 6. In requiring a demonstration that the *exact* outcome would have seemed "likely" – and not just within a likely *range* of desirable results motivating the experiment – the Federal Circuit set the bar for a § 103 challenge far too high.

Yet respondents have followed suit. They contend that "predictability [i]s an essential attribute" of obviousness. BIO 19. If (as respondents contend) predictability is *necessary* to invalidate a patent under § 103, then the contrapositive is also true: unpredictability – *any* unpredictability beyond the *de minimis* – must be sufficient to uphold it. Respondents and the Federal Circuit are both saying the same – erroneous – thing.

B. Respondents and the Federal Circuit have disregarded established legal principles. The petition explained that the proposition they advance – that an unexpected result trumps the obviousness of the path followed to reach it – clashes with this Court's prior decisions and with court of appeals decisions from before the creation of the Federal Circuit. Pet. 14-15; see, *e.g.*, *Ansonia Brass & Copper Co.* v. *Elec. Supply Co.*, 144 U.S. 11, 18 (1892) (the "application of an old process to a new and analogous purpose does not involve invention, even if the new result had not before been contemplated"); *Univ. of Ill. Found.* v. *Winegard Co.*, 402 F.2d 125, 127 (8th Cir. 1968) ("The statutory standard . . . is not 'predictability.' . . . Where logical exploration within known principles of the science achieves an unpredictable result, even though a commercially desirable one, the burden of nonobviousness is not necessarily overcome."); *Compton* v. *Metal Prods., Inc.*, 453 F.2d 38, 42 (4th Cir. 1971) ("'The ultimate question is whether a

hypothetical person having ordinary skill in the art would have readily found the same solution when addressing himself to the same problem.'").

Respondents have offered no response to this case law. And, although respondents try (at 2, 20) to divert attention from the on-point cases by citing *United States* v. *Adams*, 383 U.S. 39 (1966), that case is wholly inapposite given that the combination of elements at issue there was *not* obvious to try. See *id.* at 52 (certain "long-accepted factors, when taken together, would . . . deter any investigation into such a combination as is used by Adams").[2]

Astonishingly, Sanofi goes so far as to argue that *KSR* did not change the importance to the obviousness analysis of the "obvious to try" inquiry. BIO 27 ("*KSR* Did Not Reject the Principle that 'Obvious to Try' Is Generally Not the Standard for Obviousness."); contra 550 U.S. at 421-422 ("[T]he Court of Appeals . . . conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'"). Sanofi's agenda is to limit *KSR* so that it applies only to mechanical combinations and not to combinations of "reaction conditions and

---

[2] Sanofi also cites *Sakraida* v. *Ag Pro, Inc.*, 425 U.S. 273 (1976), and *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57 (1969), but those cases stand only for the proposition that a combination of familiar elements that "yields no more than one would expect from such an arrangement" is not patentable. BIO 20 (quoting *KSR*, 550 U.S. at 417). We do not quarrel with that principle. Rather, as the cases cited at Pet. 14-15 show, the circumstances of *Sakraida* and *Anderson's-Black Rock* are not the *only* circumstances in which a patent is invalid for obviousness.

reagents" in chemistry and other "unpredictable arts," BIO 5, 22, 29; see also pages 10-11, *infra*, but surely *KSR* is not so provincial.

C. The reason "neither lower court made any . . . factual finding," BIO 3, that Sanofi's winning experiment was "obvious to try" is that they believed that the issue was irrelevant. Pet. 9; Pet. App. 27a, 112a. Thus, in arguing (at 2, 3, 21) that the experiment was in fact not "obvious to try," respondents assume answers to the very *KSR*-mandated inquiry that the courts below refused to conduct: Was there a design need or other pressure to solve a problem and a finite number of potential solutions such that Sanofi's chemists had good reasons to test the limited and well-known "variety of procedures" and "choices of reaction conditions and reagents," BIO 5, in an effort to single out the winning combination? See Pet. 13.

Sanofi (at 21) finds it significant that the result of any given choice of reaction conditions and reagents was not predictable, but *KSR*'s reference to a finite number of "predictable solutions" cannot mean that the exact outcome of an experiment or series of experiments must be perfectly knowable in advance. (After all, an experiment whose result is truly known in advance is a pointless experiment.) Instead, *KSR* was surely referring to scenarios in which any person having ordinary skill in the art predictably would test the same *limited set of choices*. And *KSR* requires not, as Sanofi suggests, an absolute "assurance," BIO 21, 22, that two enantiomers can be successfully isolated, but rather only a reasonable "anticipat[ion]," 550 U.S. at 421, that this is true.

Likewise, as regards salt formation, see Pet. 5 n.1, 6-7 n.2, it may be true that a person of skill in the art

would not have bet that the bisulfate form of the salt would turn out to be the most useful one. See BIO 10-11, 23. That is very different, however, from saying that the prior art deterred the investigation, see *Adams*, 383 U.S. at 52, that led to the bisulfate salt. So long as the person of ordinary skill had reasons to test a given set of acids that included sulfuric acid – and that point seems undisputed[3] – obviousness should not be defeated by the supposed unexpectedness of the identity of the winning substance, or of its properties.

Ultimately, respondents' analytical flaw is to assume that an inability to predict which one of a manageable number of known possibilities will work (even if it is reasonably likely that *one* of them will work) makes it not obvious to try the full set of possibilities. That is not the law.

II. The Federal Circuit Is Intractably Inconsistent

Respondents say that our "cynical assertion that case outcomes 'depend in large part on who the panelists are' . . . do[es] not withstand a methodical review." BIO 27-28. Unfortunately, it does. The 13 modern Federal Circuit cases discussed by petitioners and respondents in this connection (including this

---

[3] See Pet. App. 73a (explaining that "the approach taken at Sanofi" to the identification of a suitable salt – namely, testing a large array of acids on the FDA-approved list, including many strong acids like sulfuric acid – was the same approach that a person of ordinary skill in the art would have used); see also *id.* at 74a ("[A] person of ordinary skill in the art would have known that . . . sulfuric acid [was one of] the three strongest acids used in pharmaceutical salts.").

case)[4] are divided almost evenly between decisions upholding and decisions invalidating patents on obviousness grounds. Yet, among those cases, there is not a single vote by any of the three panelists below to invalidate a patent for obviousness. On the contrary, in the relevant universe of cases, those three judges have each consistently voted to uphold (or to reverse a district court's or a panel's invalidation of) every one of the multiple patents they have been faced with.

Respondents contend that the Federal Circuit has "consistently held" that "unexpected and unpredictable results . . . are not automatically conclusive." BIO 24. In support of that assertion they cite *Pfizer* (as well as *Süd-Chemie*, 554 F.3d at 1009, which merely cites *Pfizer*). BIO 24-25. In *Pfizer*, however, two of the judges who decided this case wanted to rehear and reverse the panel decision because, on facts very similar to those at issue here, the *Pfizer* panel found obviousness using the "obvious-to-try" analysis endorsed by *KSR* and ignored by the panel

---

[4] See BIO 24-25, 27-28 and Pet. 18-20 & n.6, 24 n.9 (citing *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, reh'g denied, 488 F.3d 1377 (2007); *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350 (2007); *Süd Chemie, Inc.* v. *Multisorb Techs., Inc.*, 554 F.3d 1001 (2009); *Forest Labs., Inc.* v. *Ivax Pharms., Inc.*, 501 F.3d 1263 (2007); *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293 (2007), reh'g denied (Dec. 3, 2007); *In re Kubin*, 561 F.3d 1351 (2009); *Muniauction, Inc.* v. *Thomson Corp.*, 532 F.3d 1318 (2008); *Bayer Schering Pharma AG* v. *Barr Labs., Inc.*, 575 F.3d 1341 (2009); *Abbott Labs.* v. *Sandoz, Inc.*, 544 F.3d 1341 (2008); *Ortho-McNeil Pharm., Inc.* v. *Mylan Labs., Inc.*, 520 F.3d 1358 (2008)); *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286 (2006); *Procter & Gamble Co.* v. *Teva Pharms. USA, Inc.*, 566 F.3d 989 (2009)).

in this case. If this case and *Pfizer* had each been heard by the other's panel, each would have come out the other way. See Pet. 18-20.

These panel-dependent outcomes are possible only because some judges, like Sanofi (see BIO 22, 29), believe that *KSR*'s teachings on "obvious to try" apply differently or not at all in the so-called "unpredictable arts." We acknowledge that the Federal Circuit has sometimes gotten this issue right. It is impossible, however, to maintain seriously that there are not deep differences between Federal Circuit panels composed of different judges (and between the PTO and some Federal Circuit panels). Nor has the full Federal Circuit (which has had many opportunities to fix this situation) shown any inclination to reconcile its divergent cases. As we have explained, these inconsistencies create tremendous uncertainty in an area of the law where clarity and predictability are essential. See Pet. 20-21.

III. The Petition Raises A Public Policy Issue of Profound Importance

A. Respondents say that the '265 patent does not extend the monopoly on a patented compound already on the market. BIO 29. But that is exactly what it has done. The earlier '596 patent (whose validity is not disputed) claimed not just PCR4099 but its enantiomers and their salts. Pet. 5. It is undisputed that, even without the '265 patent, the earlier patent would have rewarded respondents with many profitable years of market exclusivity for Plavix. The only function of the '265 patent has been to extend Sanofi's monopoly by eight years, with no corresponding social benefit. See Pet. 16-17. As petitioners and their *amici* have explained, the economic and

medical consequences of gratuitously delaying generic competition in this fashion are gigantic. Br. of *Amici Curiae* AARP et al. 1-4, 10-13; Pet. 23, 24.

Sanofi attempts to justify this abuse by referring, mantra-like, to the "years of effort" and "tens of millions of dollars" it spent to develop the racemate. BIO 3-4, 7, 9, 23, 29-30. That is the same mistake that the Federal Circuit made, and it contributes to the necessity of further review. Pet. 21. As petitioners have pointed out (with no response from respondents), "sweat of the brow" is not and never has been the criterion for patentability. *Ibid.*

More fundamentally, the racemate and its enantiomers were already disclosed in (among other places) the prior-art '596 patent. See Pet. 6. The earlier investments were thus protected by the earlier patents. See Pet. 16, 21-22. Respondents seem to forget that the obviousness inquiry is whether "*the differences between the subject matter sought to be patented and the prior art* are such that the subject matter as a whole would have been obvious *at the time the invention was made* to a person having ordinary skill in the art." 35 U.S.C. § 103 (emphasis added). See also *Graham* v. *John Deere Co.*, 383 U.S. 1, 17 (1966) ("Under § 103, the scope and content of the prior art are to be determined; *differences between the prior art and the claims at issue are to be ascertained*; and the level of ordinary skill in the pertinent art resolved." (emphasis added)). The validity of the '265 patent properly turns not on the size of Sanofi's investment in research and development since the 1970s, but on whether, *given that PCR4099 and its enantiomers were already disclosed*, one of the enantiomers *in*

isolation would have been obvious within the meaning of § 103.

Respondents also lose sight of the fact that the obviousness inquiry is an objective one. The actions of Sanofi's own chemists (including how much time they spent on which experiments), and Sanofi's subjective characterizations of the difficulty of each experiment are beside the point. Cf. *KSR*, 550 U.S. at 420 ("The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art."). Just as "[p]atentability shall not be *negatived* by the manner in which the invention was made," 35 U.S.C. § 103 (emphasis added), so too "the manner in which the invention was made" cannot possibly *confer* patentability.

B. Sanofi implies (at 28-30) that *KSR*'s lessons somehow carry less force in the life and chemical sciences because "unpredictability here is the rule, not the exception." It is critical, however, to remember *KSR*'s bottom-line message: "As progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts." 550 U.S. at 427. See Pet. 15-17.

That message is no less applicable in the life and chemical sciences. Even in fields in which "unpredictability is the rule," there is such a thing as "ordinary innovation" and improvements that are "expected in the normal course." See Pet. 22-23. As the Federal Court of Australia recently explained in

ruling that the Australian counterpart of the '265 patent was obvious:

> Trial and error are normal, everyday parts of laboratory work and non-inventive laboratory experiments. That is what the hypothetical skilled worker in a laboratory does – *if the outcomes of experiments were known, there would be little point in doing them. That is the nature of everyday, non-inventive, research.*

Addendum, *infra*, 82 (emphasis added); see also *id.* at 19 ("Trial and error in the choice of salts involved non-inventive laboratory experiments."). The Australian court invalidated Sanofi's patent on clopidogrel bisulfate because it recognized what the Federal Circuit did not: Patents are not supposed to reward "normal, everyday" experimental work (the kind that yields "advances that would occur in the ordinary course," 550 U.S. at 419), even if aspects of that work are inherently unpredictable.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

ROBERT B. BREISBLATT
Katten Muchin Rosenman LLP
525 W. Monroe Street
Chicago, IL 60661
(312) 902-5200

ROBERT S. SILVER
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street 11th Floor
Philadelphia, PA 19103
(215) 567-2010

ROY T. ENGLERT, JR.
Counsel of record
DANIEL R. WALFISH
Robbins, Russell, Englert, Orseck, Untereiner & Sauber LLP
1801 K Street, N.W. Suite 411
Washington, D.C. 20006
(202) 775-4500

SHASHANK UPADHYE
Apotex, Inc.
150 Signet Drive
Toronto, ON M9L 1T9
Canada
(416) 401-7701

OCTOBER 2009

ADDENDUM

FEDERAL COURT OF AUSTRALIA

Apotex Pty Ltd v Sanofi-Aventis [2009] FCAFC 134

PATENTS – application for revocation – validity – claim to *d*-enantiomer (clopidogrel), pharmaceutically acceptable salts and addition salts of *d*-enantiomer, pharmaceutical compositions containing *d*-enantiomer and a process for preparation of *d*-enantiomer – prior art patents describe and claim the racemate and the enantiomers process for obtaining enantiomers well known and non-inventive – whether disclosure of salts of the racemate discloses salts of the enantiomers – whether *d*-enantiomer novel – whether pharmaceutically acceptable salts and addition salts of the *d*-enantiomer novel – whether pharmaceutical compositions containing *d*-enantiomer novel – selection patents – whether claims obvious and lack inventive step – starting point for applying common general knowledge of skilled addressee – "problem and solution" approach – whether claims valid as a manner of manufacture

Patents Act 1990 (Cth), s 138(3)
Patents Act 1952 (Cth), s 40

Advanced Building Systems Pty Limited v Ramset Fasteners (Aust) Pty Limited (1998) 194 CLR 171 cited

Aktiebolaget Hässle v Alphapharm Pty Limited (2002) 212 CLR 411 considered

Apotex Pty Limited (formerly GenRx Pty Ltd) v Sanofi-Aventis (2008) 78 IPR 485 affirmed in part

Re Beecham Group Ltd's (Amoxycillin) Application [1980] 97 RPC 261 cited

Biogen Inc v Medeva plc (1996) 36 IPR 438 cited

Bristol-Myers Squibb Company v FH Faulding & Co Limited (2000) 97 FCR 524 cited

General Tire & Rubber Company v Firestone Tyre and Rubber Company Ltd (1971) 1A IPR 121 cited

Hill v Evans (1862) 1A IPR 1 considered

H Lundbeck A/S v Alphapharm Pty Ltd (2009) 81 IPR 228 considered

Re IG Farbenindustrie AG's Patents (1930) 47 RPC 289 cited

Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd (2008) 78 IPR 20 considered

Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2) (2007) 235 CLR 173 considered

Merck & Co Inc v Arrow Pharmaceuticals Ltd (2006) 154 FCR 31 cited

Minnesota Mining and Manufacturing Company v Beiersdorf (Australia) Limited (1980) 144 CLR 253 cited

National Research Development Corporation v Commissioner of Patents (1959) 102 CLR 252 cited

Nicaro Holdings Pty Limited v Martin Engineering Co (1990) 91 ALR 513 referred to

NV Philips Gloeilampenfabrieken v Mirabella International Pty Limited (1995) 183 CLR 655 cited

Olin Corporation v Super Cartridge Co Pty Ltd (1977) 180 CLR 236 cited

Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC (2008) 77 IPR 449 considered

Wellcome Foundation Limited v VR Laboratories (Aust) Proprietary Limited (1981) 148 CLR 262 cited

APOTEX PTY LTD (ACN 096 916 148) v SANOFI-AVENTIS, SANOFI-AVENTIS US LLC and BRISTOL-MYERS SQUIBB INVEST CO LLC

NSD 1311 of 2008

SANOFI-AVENTIS, SANOFI-AVENTIS US LLC and BRISTOL-MYERS SQUIBB INVESTCO LLC v SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)

NSD 1408 of 2008

EMMETT, BENNETT & MIDDLETON JJ
29 SEPTEMBER 2009
SYDNEY

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION **NSD 1311 of 2008**

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN:	**APOTEX PTY LTD (ACN 096 916 148) Appellant**
AND:	**SANOFI-AVENTIS First Respondent**
	SANOFI-AVENTIS US LLC Second Respondent
	BRISTOL-MYERS SQUIBB INVEST CO LLC Third Respondent
JUDGES:	**EMMETT, BENNETT & MIDDLETON JJ**
DATE OF ORDER:	**29 SEPTEMBER 2009**

WHERE MADE: SYDNEY

THE COURT DIRECTS THAT:

1. The parties consult and submit jointly agreed proposed orders (including as to costs) to give effect to these reasons by 6 October 2009 or, if the parties are unable to agree on proposed orders, each party submit proposed orders by 6 October 2009.

Note: Settlement and entry of orders is dealt with in Order 36 of the Federal Court Rules. The text of entered orders can be located using eSearch on the Court's website.

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION NSD 1408 of 2008

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN:	**SANOFI-AVENTIS** **First Appellant**
	SANOFI-AVENTIS US LLC **Second Appellant**
	BRISTOL-MYERS SQUIBB INVESTCO LLC **Third Appellant**
AND:	**SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)** **Respondent**

JUDGES: **EMMETT, BENNETT & MIDDLETON JJ**

DATE OF ORDER: **29 SEPTEMBER 2009**

WHERE MADE: **SYDNEY**

THE COURT ORDERS THAT:

1. The parties consult and submit jointly agreed proposed orders (including as to costs) to give effect to these reasons by 6 October 2009 or, if the parties are unable to agree on proposed orders, each party submit proposed orders by 6 October 2009.

Note: Settlement and entry of orders is dealt with in Order 36 of the Federal Court Rules. The text of entered orders can be located using eSearch on the Court's website.

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION **NSD 1311 of 2008**

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN: **APOTEX PTY LTD (ACN 096 916 148)**
Appellant

AND: **SANOFI-AVENTIS**
First Respondent

SANOFI-AVENTIS US LLC
Second Respondent

BRISTOL-MYERS SQUIBB INVEST CO LLC
Third Respondent

IN THE FEDERAL COURT OF AUSTRALIA
NEW SOUTH WALES DISTRICT REGISTRY
GENERAL DIVISION **NSD 1408 of 2008**

BETWEEN:	**SANOFI-AVENTIS** **First Appellant**
	SANOFI-AVENTIS US LLC **Second Appellant**
	BRISTOL-MYERS SQUIBB INVESTCO LLC **Third Appellant**
AND:	**SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)** **Respondent**
JUDGES:	**EMMETT, BENNETT & MIDDLETON JJ**
DATE:	**29 SEPTEMBER 2009**
PLACE:	**SYDNEY**

REASONS FOR JUDGMENT

EMMETT J

INTRODUCTION

1 These two appeals are concerned with the validity of Australian Patent Number 597784 (**the Patent**), which is registered in the name of Sanofi-Aventis (**Sanofi**). Sanofi-Aventis US LLC (**Sanofi US**) and Bristol-Myer Squidd Invest Co

LLC (**Bristol-Myers**) are licensees of the Patent, as members of the Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (**the Partnership**). The Patent relates to a series of products and processes principally concerned with the compound consisting of one of the enantiomers of a racemate compound designated PCR 4099 (**PCR 4099**). The enantiomer in question (**the d-enantiomer**) has the international non-proprietary name Clopidogrel.

2 PCR 4099 was disclosed and claimed in Australian Patent Number 554358 (**the Australian 4099 Patent**). The Australian 4099 Patent, which is also registered in the name of Sanofi, relates to new thieno (3, 2-c) pyridine derivatives, their process of preparation and their therapeutic application in inhibiting thrombosis or clot formation in blood.

3 Apotex Pty Limited (**Apotex**) commenced a proceeding in the Court claiming an order that the Patent and all claims of the Patent be revoked (**the Apotex Proceeding**). Sanofi and the Partnership filed a cross-claim in that proceeding seeking orders restraining Apotex from infringing the Patent. Subsequently, Spirit Pharmaceuticals Pty Ltd (**Spirit**) also commenced a proceeding in the Court seeking revocation of the Patent (**the Spirit Proceeding**). The Apotex Proceeding, including the cross-claim, and the Spirit Proceeding were heard together and on 19 August 2008 a judge of the Court made orders in both proceedings.

4 The Patent has eleven Claims. The primary judge held that Claim 1 and Claims 6 to 11 were invalid. His Honour concluded that Claim 1 is invalid on the ground of lack of novelty and that Claims 10 and 11, as presently framed, fall with Claim 1. His Honour also held that Claims 6 to 9 were invalid on the ground of lack of inventive step. However, his Honour rejected all other grounds of invalidity in relation to those Claims and rejected all grounds of invalidity in respect of Claims 2 to 5. Accordingly, his Honour found that Claims 2 to 5 are valid.

5 On 19 August 2008, Apotex filed a notice of appeal (**the Apotex Appeal**) from certain of the orders made by the primary judge in the Apotex Proceeding and, on 8 September 2008 Sanofi and the Partnership filed a notice of cross-appeal (**the Cross Appeal**) from other orders made by the primary judge in that proceeding. On the same day, Sanofi and the Partnership filed a notice of appeal (**the Sanofi Appeal**) from orders made in the Spirit Proceeding.

6 In the Apotex Appeal, Apotex appeals from so much of the orders of the primary judge as failed to determine that Claims 2 to 5 are invalid. In the Cross Appeal and in the Sanofi Appeal, Sanofi and the Partnership appeal from the orders of the primary judge revoking Claim 1 and Claims 6 to 11. Spirit is the respondent in the Sanofi Appeal and supports the position adopted by Apotex in relation to each of the Claims. It has also filed notice of contention seeking to support the determinations of the primary judge in the Spirit Proceeding on different grounds.

THE CHEMISTRY

7 I have taken the following brief description of the relevant chemistry from the reasons of the primary judge. The parties did not suggest that there was any relevant inaccuracy in his Honour's findings.

8 The claimed invention of the Patent relates to organic chemistry, which is concerned with the study of carbon compounds and, in particular, with the **stereochemistry** of carbon compounds in relation to the three dimensional structure of their molecules. **Isomers** are compounds whose molecules consist of the same number and kind of atoms but differ in their structure or arrangement. Some compounds are said to be **optically active**. The means of identifying compounds that have such a property is to shine a plane of polarised light through a sample of the compound dissolved in an appropriate solvent. The extent of the rotation is then measured. Display of optical activity by a compound indicates that the chemical structure of a molecule of that compound is non-superimposable on its mirror image. That property is called **chirality** and the molecule is described as **chiral**. An organic compound is said to have a **chiral centre** if it includes a carbon atom bonded to four different substitutes.

9 Where there is optical activity, there are two, and only two, isomers, called **enantiomers**. The enantiomers differ in structure such that the arrangements of their atoms in space are non-superimposable mirror images of each other.

Enantiomers have identical physical and chemical properties except in two important respects. First, they rotate the plane of polarised light in opposite directions, though to the same extent. Secondly, they interact in different ways with other chiral compounds, including reacting with them at different rates. The isomer that rotates the plane of polarised light to the left, or counter-clockwise, is called the levo isomer or levo-rotary or l-enantiomer, and is designated (-). The other isomer, which rotates the plane of polarised light to the right, or clockwise, is called the dextro isomer, or dextro-rotary or d-enantiomer, and is designated (+).

10 A pure compound is always optically active if it is composed of chiral molecules. However, a mixture of equal amounts of enantiomers of the same compound will be optically inactive, since the equal and opposite rotations of the two enantiomers cancel each other out. A mixture comprised of equal amounts of the two enantiomers is called a **racemate** or a **racemic mixture** and is often designated by the prefix (+/-). The separation of a racemic mixture into its two optically active enantiomers is called **resolution**. The chemical formula of each enantiomer and of their racemic mixture is the same.

11 The salt of a chemical compound can be formed by combining an acid with a base. An acidic compound is characterised by its ability to donate a proton to its surroundings whereas a basic compound is characterised by its ability to

accept a proton from its surroundings. Salts may form a crystalline compound.

12 The **pharmacological** properties of a compound are concerned with the operation of the compound in a biological system *in vivo*. That involves the efficacy, tolerance and toxicity of the compound as a pharmaceutical drug. The claimed invention of the Patent is applied to biological systems, which are composed of chiral molecules. Because enantiomers interact with other chiral molecules in different ways, they will often behave differently in a biological system. That can result in the enantiomers having different physiological effects, manifested in the efficacy, tolerance and toxicity of the compound as a pharmaceutical drug.

THE PATENT AND ITS CLAIMS

13 The claimed invention of the Patent is primarily Clopidogrel. After obtaining regulatory approval, Sanofi launched a product under the name Plavix in 1998. The active ingredient of Plavix is the bisulphate salt of Clopidogrel. Plavix has been commercially successful. It inhibits platelet aggregation in the site of blood vessel damage, and so inhibits thrombosis or clot formation.

14 Claim 1 of the Patent is for the d-enantiomer of PCR 4099, namely, Clopidogrel. The l-enantiomer is said to be inactive and less well tolerated than the d-enantiomer. The claimed invention also relates to salts of the d-enantiomer produced by the addition of a pharmaceutically

acceptable mineral or organic acid. Thus, Claim 1 is for the d-enantiomer and its pharmaceutically acceptable salts and Claims 2, 3, 4 and 5 are respectively for the hydrochloride salt, the hydrogen sulfate or bisulphate salt, the hydrobromide salt and the taurocholate salt.

15 The specification of the Patent says that the d-enantiomer can be prepared by forming the salt of PCR 4099 with an optically active acid in a solvent, repeated crystallisations of the salt until a product of constant optical rotatory power is obtained, followed by the liberation of the d-enantiomer from its salt by a base. If required, a salt is formed between the d-enantiomer and a pharmaceutically acceptable acid. That process is the subject of Claim 6. Claim 7 is for the process described in Claim 6 using a specified acid as the optically active acid. Claim 8 is for the process of Claim 6 or Claim 7 with the performance of re-crystallisations from acetone. Claim 9 is for the process of Claim 6, Claim 7 or Claim 8 with the formation of a salt in acetone.

16 Claim 10 is for a pharmaceutical composition in which the active ingredient is one or other of the compounds described in Claim 1 to Claim 5 inclusive, together with a pharmaceutically acceptable carrier. Claim 11 is for the pharmaceutical composition of Claim 10 with a specific unit dose of from 0.001 g to 0.100 g of the active ingredient.

THE EARLIER PATENTS

17 The specification of the Patent refers to French Patent No. 2530247 (**the French 4099 Patent**) as having described PCR 4099. The Australian 4099 Patent claims priority from the French 4099 Patent. They are in substantially identical terms. Canadian Patent No. 1194875 (**the Canadian 4099 Patent**) also claims priority from the French 4099 Patent. Sanofi is the registered proprietor of each of the Australian 4099 Patent, the French 4099 Patent and the Canadian 4099 Patent (together the **Earlier Patents**).

18 Apotex and Spirit rely on the ground that the Patent is not novel having regard to the disclosure in the Australian 4099 Patent, the French 4099 Patent and the Canadian 4099 Patent. The Australian 4099 Patent was open to public inspection in Australia on 19 January 1984. The French 4099 Patent was open to public inspection in Australia on 15 March 1984 and the Canadian 4099 Patent was open to public inspection in Australia on 7 November 1985.

THE VALIDITY OF THE CLAIMS

19 It is convenient to deal with the claims in four groups as follows:

- Claim 1.
- Claims 2 to 5.
- Claims 6 to 9.
- Claims 10 and 11.

Claim 1

20 I agree with the conclusion reached by Bennett and Middleton JJ, for the reasons given by their Honours, that there was a disclosure, in the Earlier Patents of the enantiomers of PCR 4099, including the d-enantiomer of the Patent. The enantiomers were expressly claimed. The Earlier Patents disclosed the enantiomers as part of the invention and as compounds predicted to have the relevant beneficial qualities. The relevant skilled addressee of the Earlier Patents would understand to separate the enantiomers and would know the methods to apply. The preparation of the enantiomers was routine and involved no inventive step. Claim 1, in so far as it claims the d-enantiomer, is invalid.

21 Claim 1 extends also to the pharmaceutically acceptable salts of the d-enantiomer. I shall deal with that aspect of Claim 1 when dealing with Claims 2 to 5.

Pharmaceutically Acceptable Salts of Claim 1 and Claims 2 to 5

22 In addition to claiming the d-enantiomer, Claim 1 is also for pharmaceutically acceptable salts of the d-enantiomer. Further, each of Claims 2 to 5 is for a particular salt of the d-enantiomer. Claim 2 narrows Claim 1 by limitation to the hydrochloride salt. Claim 3 narrows Claim 1 by limitation to the hydrogen sulphate, or bisulphate, salt. Claim 4 narrows Claim 1 by limitation to the hydrobromide salt. Claim 5

narrows Claim 1 by limitation to the taurocholate salt.

23 The primary judge found that it was known at the priority date of the Patent that a pharmaceutically acceptable salt was useful for administration of an active compound. Further, the acids chosen in Claims 2 to 5 were conventional and standard methods for their preparation were known at the priority date.

24 The Earlier Patents refer to salts of the compounds disclosed with pharmaceutically acceptable mineral or organics salts. For example, the Canadian 4099 Patent states that the invention also includes:

> the addition salts with pharmaceutically acceptable mineral or organic acids.

Claim 1 of the Canadian 4099 Patent employed the same language. Further, in three different places, Claim 1 of the Canadian 4099 Patent says:

> then the derivative sought is obtained, which is isolated and, if desired, **its** enantiomers are separated and/or **it** is salified by mineral or organic acid action.

In addition, Claim 14 of the Canadian 4099 Patent refers to:

> their addition salts with pharmaceutically acceptable mineral or organic acids.

25 Prior to 1987, hydrochloric acid and sulphuric acid were common laboratory acids and were used to make pharmaceutical salts. Thus, the relevantly skilled addressee would understand the statement of the invention in the Earlier Patents as including a disclosure of addition salts of the compounds, and their enantiomers, with hydrochloric and sulphuric acid.

26 The Canadian 4099 Patent clearly discloses that the invention includes the addition salts with pharmaceutically acceptable mineral or organic acids. It claimed for a process for the preparation of derivatives of the general formula described, and the addition salts of those derivatives with pharmaceutically acceptable mineral or organic acids, whereby a derivative is made and isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid. The reference to **it** being salified is, as a matter of syntax, a reference to the salifaction of the relevant derivative.

27 The Canadian 4099 Patent proffers non-limiting examples to illustrate the invention claimed in that patent. Examples 1, 2, 3 and 13 involve hydrochloride, examples 4, 7, 8 and 9 involve bisulphate and example 10 involves hydrobromide. Thus, the examples disclose addition salts of compounds covered by the general formula disclosed, together with well known mineral acids such as HCl, H_2SO_4 and HBr. There is a clear disclosure of PRC 4099 and its enantiomers, including the d-enantiomer. The skilled addressee would know that that would

include salts with the well known acids HCl, H_2SO_4 and HBr, which are expressly exemplified in the body of the specification.

28 In the light of the earlier Patents, there are quite cogent reasons for concluding that the claim in Claim 1 for pharmaceutically acceptable salts and the claims in Claims 2 to 4 for particular salts of the d-enantiomer are not novel. Thus, the Canadian 4099 Patent effectively directs the skilled addressee to make the hydrochloric, sulphuric and hydrobromic salts of the derivatives of the general formula. One of those derivatives is PCR 4099. The addressee is invited to separate the enantiomers. The reference to salification of the derivatives is an effective disclosure of the salts of the enantiomers made with those acids. That does not require the exercise of any inventive ingenuity or the taking of any inventive step (see *Nicaro Holdings Pty Limited v Martin Engineering Co* (1990) 91 ALR 513 at 531). However, having regard to the conclusion I have reached in relation to lack of inventive step, it is not necessary to form a firm view on the question of novelty in relation to salts of the d-enantiomer.

29 I agree with Bennett and Middleton JJ, for the reasons given by their Honours, that neither the pharmaceutically acceptable salts of the d-enantiomer nor the specific salts of Claims 2 to 5 involved an inventive step, in the light of the common general knowledge as at the priority date of the patent. The common general knowledge included the fundamental principles of stereochemistry, methods for obtaining individual

enantiomers from a racemate and the formation of salts of stereochemical compounds for pharmaceutical purposes.

30 In particular, information concerning diastereomeric salt formation was well known prior to 1987 as a well developed method. Choices were involved, including choices of chiral resolving agent, acid or base as required, and solvent. While trial and error experimentation may have been required, the experimentation was not such as went beyond routine experimentation. The formation of pharmaceutically acceptable salts of both racemates and enantiomers was a common process prior to 1987 and the techniques for that process were known. While a choice was to be made in relation to which salt would be made, a process involving trial and error, and a choice was to be made in terms of acid, both hydrochloric and sulphuric acid were common laboratory acids used to make pharmaceutical salts prior to 1987.

31 The specification of the Patent does not claim an inventive step in the method of obtaining the salts, once the d-enantiomer was known. It was known that a pharmaceutically acceptable salt was useful for administration of an active compound and it was known how to prepare such salts using known mineral or organic acids. Further, the primary judge found that the acids chosen were conventional and that standard methods of preparation were known.

32 The primary judge found that all of the acids used to make the salts of Claims 2 to 5, namely,

hydrochloric acid, sulphuric acid, hydrobromic acid and taurochloric acid, were conventional. Trial and error in the choice of salts involved non-inventive laboratory experiments. Thus, a non-inventive worker in the field, seeking to make a pharmaceutically acceptable salt of the d-enantiomer, on the basis of the unchallenged findings of the primary judge, chose an acid that was readily available and commonly and conventionally used. The non-inventive skilled worker would have been led directly to the salts of Claims 2 to 5 and would apply common processes and techniques to make pharmaceutically acceptable salts of the d-enantiomer including the salts of Claims 2 to 5.

33 It follows that no inventive step was involved in the claim to pharmaceutically salts. Further, no inventive step was involved in the claim for the four specific salts of Claims 2 to 5 inclusive.

Claims 6 to 9

34 Claim 6 is for a process for the preparation of the compound of Claim 1. Claim 7 is based on Claim 6. Claim 8 is dependent upon Claims 6 or 7 and Claim 9 is dependent upon Claims 6, 7 or 8. Thus, Claims 7, 8 and 9 fall with Claim 6.

35 The desire to obtain the compound of Claim 1, the d-enantiomer, is taken for granted. That is to say, the claim is for the means of obtaining the d-enantiomer, not for the decision to do so. The primary judge found that the method used to obtain the compound of Claim 1 was well known in the field in Australia as at the priority date.

Further, his Honour also found that each of the additional integers of Claims 7, 8 and 9 was well known at the priority date and that there were no circumstances to make inventive the choice of the known process described. There was no inventive step in ascertaining the pharmacological characteristics of the enantiomers. The primary judge found that the method of resolution was well known as a means of obtaining enantiomers of a racemic compound as was the chiral resolving agent used.

36 I agree with Bennett and Middleton JJ, for the reasons given by their Honours, that there was no error on the part of the primary judge in concluding that Claims 6 to 9 lacked an inventive step.

Claims 10 and 11

37 Claim 10 is for a pharmaceutical composition comprising, as active ingredient, a compound according to one of Claims 1 to 5, together with a pharmaceutically acceptable carrier. Claim 10 as drafted must fail in so far as it claims a composition comprising as active ingredient the compounds of Claims 1 to 5. The same reasoning applies to Claim 11, which is for a composition according to Claim 10 comprising specified doses of active ingredient.

38 I agree with the conclusion reached by Bennett and Middleton JJ, for the reasons given by their Honours, that there was a disclosure, in

the Earlier Patents, of the active ingredient of that invention with a pharmaceutically acceptable carrier. As indicated above, the Canadian 4099 Patent discloses the d-enantiomer of PCR 4099, the compound of Claim 1 of the Patent. The unit doses of Claim 11 of the Patent are disclosed in the Canadian 4099 Patent.

39 It follows that Claims 10 and 11 are invalid. That was the conclusion reached by the primary judge.

CONCLUSION

40 It follows that all claims of the Patent are invalid. The Patent should be revoked in its entirety. The parties have asked the Court to defer ruling on the question of costs until the substantive questions have been determined.

I certify that the preceding forty (40) numbered paragraphs are a true copy of the Reasons for Judgment herein of the Honourable Justice Emmett.

Associate: /s/

Dated: 29 September 2009

IN THE FEDERAL COURT OF AUSTRALIA

NEW SOUTH WALES DISTRICT REGISTRY

GENERAL DIVISION **NSD 1311 of 2008**

ON APPEAL FROM A SINGLE JUDGE OF THE FEDERAL COURT OF AUSTRALIA

BETWEEN: **APOTEX PTY LTD (ACN 096 916 148)**
Appellant/Cross-Respondent

AND: **SANOFI-AVENTIS**
First Respondent/ Cross-Appellant

SANOFI-AVENTIS US LLC
Second Respondent/ Cross-Appellant

BRISTOL-MYERS SQUIBB INVESTCO LLC
Third Respondent/ Cross-Appellant

IN THE FEDERAL COURT OF AUSTRALIA

NEW SOUTH WALES DISTRICT REGISTRY

GENERAL DIVISION **NSD 1408 of 2008**

BETWEEN: **SANOFI-AVENTIS**
First Appellant

SANOFI-AVENTIS US LLC
Second Appellant

	BRISTOL-MYERS SQUIBB INVESTCO LLC **Third Appellant**
AND:	**SPIRIT PHARMACEUTICALS PTY LTD (ACN 109 225 747)** **Respondent**
JUDGES:	**EMMETT, BENNETT AND MIDDLETON JJ**
DATE:	**29 SEPTEMBER 2009**
PLACE:	**SYDNEY**

REASONS FOR JUDGMENT

BENNETT AND MIDDLETON JJ

41 Apotex Pty Ltd ('Apotex') and Spirit Pharmaceuticals Pty Ltd ('Spirit') seek revocation of Australian Patent No 597784 ('the Patent') pursuant to s 138(3) of the *Patents Act 1990* (Cth) ('the 1990 Act'). Broadly speaking, the Patent claims an enantiomer of a racemate, a process for its preparation and the pharmaceutical compositions containing it. The racemate, designated PCR 4099, was disclosed and claimed in earlier patents filed by the same patentee, Sanofi-Aventis ('Sanofi'), and by its related companies.

42 The grounds relied upon for revocation that are pressed in the appeal are:

- Lack of novelty;
- Lack of inventive step; and
- Not a manner of manufacture.

THE CHEMICAL BACKGROUND

43 The primary judge, at [4] to [11], set out a detailed chemical background which is not in dispute. The relevant matters to note are:

- A racemate, or racemic mixture, consists of two enantiomers, the (+) (dextro) or d-enantiomer and the (-) (levo) or l-enantiomer, in the proportion of 50-50. A racemic mixture consists, statistically, of equal proportions of the two enantiomers.

- A racemate and its enantiomers have the same chemical formula but the enantiomers differ in their structure such that the arrangement of their atoms in space is as non-superimposable mirror images. It is the three-dimensional structure that distinguishes one enantiomer from the other.

- Enantiomers have identical physical and chemical properties except in two important respects:

    1. Enantiomers are optically active and the designation of an enantiomer as (+) (dextro) (d) or (-) (levo) (l) depends on the way in which it rotates polarised light. Enantiomers rotate the plane of polarised light in opposite directions, although in equal amounts.

    2. Enantiomers interact in different ways with other optically active compounds, including reacting with them at different rates. This can result in the enantiomers having different physiological effects, as

to efficacy and toxicity. The relevant physiological activity in this case is inhibition of blood-platelet aggregation.

- It is not possible to designate an enantiomer as (+) or (-) or to determine its properties until the enantiomer is obtained, the plane of polarised light is shone through a sample of the compound dissolved in an appropriate solvent and the extent of the rotation is measured.
- The separation of a racemic mixture, designated (±), into its two optically active enantiomers is called resolution. One process of resolution is diastereomeric salt formation.
- An enantiomer may undergo racemisation (convert to a 1:1 mixture of both enantiomers) *in vivo*.

The enantiomers of PCR 4099

44 Sanofi commenced work on a class of compounds called thienopyridines in 1972. A number of compounds were discovered and developed which ultimately, in July 1980, led to the synthesis of a racemic compound called PCR 4099. Test results indicated that PCR 4099 was better tolerated and more effective than the previously marketed compound. It was one of 21 compounds of the same general formula that were synthesised by Sanofi from about 1976 until 1980. Patents were obtained in various countries, including Australia, France, the United States of

America ('the US') and Canada, in respect of the compounds of that general formula ('the prior art patents'). The Australian prior art patent, with a priority date of 13 July 1982, identified PCR 4099 as example 1 or derivative No 1. The French, Australian and US prior art patents had the same language and description; the Canadian prior art patent was somewhat different.

45 Between 1983 and 1985, development and testing of PCR 4099 resulted in reports of side effects in some animals. In or about November 1985 Sanofi decided to attempt to obtain the enantiomers of that compound. After a number of unsuccessful attempts, Mr Badorc of Sanofi obtained, first, the l-enantiomer of PCR 4099 by diastereomeric salt formation and then the d-enantiomer.

46 Testing of the two enantiomers indicated that the d-enantiomer had all the activity. That is, the d-enantiomer exhibited the same biological activity as the racemic mixture with half the dose. The l-enantiomer had no activity and, further, was less well-tolerated. Indeed, it proved to be more than twice as toxic as the active d-enantiomer.

47 There is no need to recite the chemical background to the claimed invention. It is sufficient to restate a number of propositions that were not in dispute:

- The skilled reader would, as at the priority date, have understood that the compounds of the prior art patents, the new thienopyridines, exist as racemates; that is,

that the chemical structure of these compounds is such that the compounds are optically active.

- The skilled reader would know, on looking at the chemical structure of PCR 4099, that it exists as a racemic mixture.
- Each of the racemate, the (+)-enantiomer and the (-)-enantiomer are properly described by that chemical structure.
- The techniques for resolving a racemate into the two enantiomers were, at the priority date, well-known.

THE PATENT

48 The Patent states that the invention "relates" to a series of products and processes. First, the invention relates to the d-enantiomer of PCR 4099.

49 Second, the invention relates to a process for the preparation of the d-enantiomer.

50 Third, the invention relates to pharmaceutical compositions containing the d-enantiomer.

51 Fourth, the invention relates to the addition salts of the d-enantiomer with pharmaceutically acceptable mineral or organic acids.

52 The specification acknowledges (at page 1(a)) that the formula provided for PCR 4099 represents both the d- and the l-enantiomer as well as the racemic mixture. The specification

acknowledges that the racemic mixture corresponding to the formula was described in the French prior art patent.

53 The specification states that, '[i]*n an unexpected manner*', only the d-enantiomer exhibits the desired activity of inhibition of platelet aggregation, the l-enantiomer being inactive. Further, it is the inactive l-enantiomer that is the less well-tolerated of the two enantiomers. The specification asserts that the preparation and purification of certain salts of the d-enantiomer has proved difficult. As a result of the asserted difficulty in the preparation and purification of the salts of the d-enantiomer, the present invention is also said to relate particularly to specified salts, being mineral and organic acid salts which, it is said, are prepared in a standard manner by the action of the corresponding acid on the base in solution in a solvent from which they precipitate spontaneously or after the addition of a non-solvent of the salt.

The claims of the Patent

54 We shall refer to the enantiomer the subject of the Patent, the dextro-rotatory enantiomer of PCR 4099, as the d-enantiomer, and the other enantiomer, the levo-rotatory enantiomer, as the l-enantiomer.

55 The claims of the Patent are to:

1. The d-enantiomer and its pharmaceutically acceptable salts.

2. The hydrochloride of the d-enantiomer.

3. The hydrogen sulphate of the d-enantiomer.

4. The hydrobromide of the d-enantiomer.

5. The taurocholate of the d-enantiomer.

6. A process for the preparation of the compound according to claim 1, comprising the formation of a salt of PCR 4099 with an optically active acid in a solvent. Repeated recrystallisations of the salt are carried out until a product of constant optical rotatory power is obtained, then the d-enantiomer is liberated from its salt by a base and, if necessary, salt formation is carried out with a pharmaceutically acceptable acid.

7. The process according to claim 6, comprising levo-rotatory camphor-10-sulphonic acid as the optically active acid.

8. The process according to one of claims 6 or 7, comprising the performance of recrystallisations from acetone.

9. The process according to one of claims 6 to 8, comprising the formation of a salt in acetone.

10. A pharmaceutical composition comprising as active ingredient one compound according to one of claims 1 to 5 together with a pharmaceutically acceptable carrier.

11. A composition according to claim 10, comprising unit doses containing from 0.001g to 0.100g of active ingredient.

The primary judge's conclusions as to the claims

56 The primary judge held that:

- Claim 1 was invalid on the ground of lack of novelty;
- Claims 10 and 11 fell with claim 1 and were, therefore, also invalid on the ground of lack of novelty;
- Claims 6 to 9 were invalid on the ground of lack of inventive step; and
- If claim 1 were novel, then it was obvious and did not involve an inventive step.

57 His Honour dismissed all other grounds of invalidity. In particular, his Honour held that claims 2 to 5 were novel and did involve an inventive step and that the invention did involve a manner of manufacture.

THE APPEAL

Sanofi's appeal

58 Sanofi appeals from the primary judge's findings that claims 1, 10 and 11 were invalid for lack of novelty and that claims 1, 6 to 9 and 10 and 11 were invalid for lack of inventive step.

Apotex's appeal

59 In essence, Apotex appeals from the primary judge's finding that claims 2 to 5 of the Patent, which claim specific salts of the d-enantiomer,

were valid. Apotex submits that the primary judge should have found that claims 2 to 5 were invalid on the grounds of lack of novelty, lack of inventive step and no manner of manufacture.

60 In addition, Apotex contends that the primary judge erred:

- In failing to hold that the pharmaceutical compositions of claims 10 and 11 did not involve an inventive step; and
- In holding that claims 1, 10 and 11 involved a manner of manufacture.

Spirit's amended notice of contention

61 Spirit submits that the primary judge was correct in holding that claims 1, 6 to 9 and 10 and 11 were invalid.

62 Spirit contends that the primary judge's decision on the question of novelty should be upheld on a number of additional bases:

1. If it is a requirement under Australian law that there be "enabling disclosure", the prior art satisfies such a requirement.
2. The principles relating to selection patents as explained in *Re IG Farbenindustrie AG's Patents* (1930) 47 RPC 289 are irrelevant to the question of anticipation.
3. If selection patents are relevant to anticipation, a valid selection patent ought not to be made from a small class as in the present case.

4. Claim 1 of the Patent ought to be found to be invalid for want of novelty because of the disclosure in the prior art patents of not only the d-enantiomer of PCR 4099 but also its pharmaceutically acceptable salts.

63 In addition, Spirit contends that the invalidity of claims 1, 10 and 11 should also be upheld on the basis of an absence of manner of manufacture and, to the extent that his Honour did not so find, on the basis of an absence of inventive step in relation to both the d-enantiomer and its pharmaceutically acceptable salts.

64 Spirit also contends that the primary judge erred in failing to hold that claims 10 and 11 did not involve an inventive step when they are dependent on claim 1.

Summary of the issues raised by the appeals

65 In summary, the issues raised by the appeals are:

1. Whether claims 1, 2 to 5 and 10 and 11 are invalid for lack of novelty, lack of inventive step and not being a manner of manufacture; and

2. Whether claims 6 to 9 are invalid for lack of inventive step.

66 The Court, in construing the claims and the prior art, does so putting itself in the position of the skilled addressee in understanding the words

and expressions used and the disclosures of those documents.

NOVELTY

67 In order to understand the submissions concerning the primary judge's findings on novelty, it is necessary to consider the prior art patents said to anticipate the inventions of the claims of the Patent.

The relevant disclosures in the prior art patents

68 The four prior art patents all relate to the same new class of thienopyridines. In each of the prior art patents, the new thienopyridines of the invention have the same general formula in which "X" and "Y" represent a range of possible atoms or other chemical groups. Broadly speaking, the prior art patents claim compounds of the general formula and certain specific derivatives thereof.

69 The prior art patents differ slightly from one another.

The Australian, French and US prior art patents

70 The Australian prior art patent states that it contains a full description of the invention, including the best method of performing it known to the patentee. It sets out the general formula of the new class of thienopyridines and a process for

the preparation of that class of compounds and describes their therapeutic applications as blood-platelet aggregation inhibitors. The patent explains that the compounds, having an asymmetrical carbon, may exist in the form of two enantiomers and continues: '*The invention relates both to each enantiomer and their mixture*'. A process for the preparation of various derivatives is described, including derivative No 1, PCR 4099. There is no process described for the preparation of the enantiomers. It is stated that pharmacological and toxicological tests demonstrate the properties of the derivatives of the invention in terms of toxicity, tolerance and activity. There are claims to the class of compounds and various of the individual derivatives. These are all racemates.

71 Claim 14 claims a therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing as active ingredient a derivative of the general formula, or an addition salt thereof, '*as well as one of the two enantiomers or their mixture*'.

72 The French and US prior art patents are relevantly in the same terms.

The Canadian prior art patent

73 The Canadian prior art patent states that the thienopyridine compounds of the general formula '*include an asymmetrical carbon which may exist in the form of 2 enantiomers. The invention also concerns each of the enantiomers and their mixture*'.

74 Claim 1 is to a process for the preparation of derivatives of general formula (I) '*as well as the 2 enantiomers or their mixture of these compounds of formula (I)*'. Claim 1 states three times during the description of the process: the '*derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified*'.

75 Claim 8 claims a process according to claim 1 for the preparation of PCR 4099. Apotex says that this "picks up" the enantiomers, although they are not specified in claim 8.

76 Claim 14 is the product claim by reference to the compounds of the general formula '*as well as the 2 enantiomers or their mixture of these compounds of formula (I); each time they are obtained by the process of claim 1*'.

What is described in the prior art patents?

77 There is no doubt that the prior art patents describe and claim the enantiomers. There is no qualification to the product claims or to the process claims. Use of the enantiomers of PCR 4099 would infringe the claims of the prior art patents.

78 There is no description of a process to obtain the enantiomers. If the claims of the prior art patents were valid and the patents were to comply with s 40 of the *Patents Act 1952* (Cth) ('the 1952 Act') and the 1990 Act, the patents seem to assume that the worker of ordinary skill did not need a description of the process of

resolution or separation of the enantiomers of the derivatives of formula (I) (including PCR 4099) in order to obtain those claimed enantiomers.

79 Sanofi points out that no process of resolution of the racemate into the constituent enantiomers, or of preparation of the individual enantiomers of the derivatives, is described and that successful separation of the enantiomers was by no means assured, even if the prior art patents contained a direction to do so. Sanofi also says that, until the enantiomers are prepared, it is not known which is the d-enantiomer and which is the l-enantiomer, nor their levels of activity and toxicity. In short, Sanofi submits that further discovery is needed before the invention claimed in the Patent is obtained.

Claim 1 of the Patent

The findings of the primary judge on the novelty of claim 1

80 The primary judge recognised that claim 1 of the Patent claims a chemical compound with a specific property, namely, the ability to rotate plane polarised light to the right. The d-enantiomer is not expressly identified as such in the French prior art patent, nor was there a suggestion that the enantiomers had been separately obtained or tested. His Honour accepted that the skilled reader of the French prior art patent would understand that the compounds there described, including PCR 4099, were racemates and that was "spelled out" in the French prior art patent. However, there was express reference in

the French prior art patent to the enantiomers in terms such as:

- "The invention relates both to each enantiomer and their mixture";
- (In claim 1) "as well as the two enantiomers or their mixture";
- (In claim 14) "as well as one of the two enantiomers or their mixture".

81 Claim 1 of the Canadian prior art patent was to a process for the preparation of derivatives of the general formula:

- "as well as the 2 enantiomers or their mixture";
- "if desired, [the derivative's] enantiomers are separated".

82 Claim 8 of the Canadian prior art patent was to a process for the preparation of PCR 4099:

- "as well as the 2 enantiomers or their mixture" (by incorporation of claim 1).

83 Claim 14 of the Canadian prior art patent was to derivatives of the general formula:

- "as well as the 2 enantiomers or their mixture".

84 The primary judge concluded that the French and corresponding prior art patents each plainly carried the claim that the enantiomers were within the compounds disclosed.

85 A number of matters are not in dispute and were accepted by the primary judge:

- The d-enantiomer is not expressly identified as such in the French prior art patent (or the other prior art patents). While the formula for the racemate and the enantiomers is the same, the stereochemistry was not defined in the prior art patents. Until the enantiomers are obtained, it cannot be predicted which enantiomer rotates plane-polarised light to the left (the l-enantiomer) and which to the right (the d-enantiomer).

- There was and is a range of potential difference in activity between enantiomers. It is not unusual for one enantiomer to display most of the activity and the other little. The activity and toxicity of the enantiomers could not be predicted with certainty until the enantiomers were separated or synthesised and tested.

- A range of techniques for obtaining enantiomers from a racemate was well-known prior to 1987, including diastereomeric salt formation. That method was straightforward and routine, although it involved choices and trial and error experimentation carrying no guarantee of success.

86 Accepting that the only compounds tested in the prior art patents were racemates, his Honour noted that the racemate and the enantiomers had identical chemical formulae and that the basis for the prior art patents was that all

compounds of the class claimed, whether exemplified or not, displayed useful activity. The compounds exemplified differed in their precise effect. No distinction was drawn in the prior art patents between the pharmacological properties of the racemate and the single enantiomers. His Honour concluded that the references to the enantiomers in the prior art patents were consistent only with a disclosure of and a claim to each enantiomer, separate from the racemate and from each other. The prior art patents claimed all compounds within the class disclosed, despite different levels of activity and whether exemplified or not. The prior art patents claimed that a broad class of compounds was effective based on a generalisation from limited results obtained with respect to some of them. That is permissible and not unusual.

87 The primary judge said, at [48], that the claims for the separate enantiomers could be described as "bare claims" for efficacy and that there was no basis for knowing what, if any, efficacy or toxicity would apply to either enantiomer of any particular racemate. His Honour concluded that the d-enantiomer was identified as a compound with useful properties concerning platelet aggregation.

88 His Honour rejected the evidence of those witnesses who denied that the claims of the prior art patents encompassed each of the separated single enantiomers as: '*to say the least, not impressive*'. The primary judge was clearly aware of the need to look at the disclosure of each of the prior art patents and the quality of that

disclosure to the skilled reader. He concluded at [63] that the invention disclosed and claimed by the French prior art patent necessarily carried the implication of a direction, recommendation or suggestion which, if followed, would result in the claimed invention, the d-enantiomer (*Bristol-Myers Squibb Company v FH Faulding & Co Limited* (2000) 97 FCR 524 at [67] per Black CJ and Lehane J).

89 The invention of the prior art patents was not described by reference to a particular result as to efficacy or toxicity and the claims were not so limited. Neither is claim 1 of the Patent. In any event, his Honour pointed out that the formula of PCR 4099 was expressly disclosed as having the claimed advantage and that the same claim was made in relation to each enantiomer of that derivative, so that the enantiomers were disclosed and claim 1 of the Patent is anticipated.

90 In summary, the primary judge noted that the formula of PCR 4099 is identical to the formula of the d-enantiomer claimed in the Patent. His Honour accepted that the skilled but not inventive reader would have understood that each derivative in the French prior art patent and corresponding prior art patents was a racemate and that the technical explanations as to the means of obtaining the derivatives and the testing of them related only to racemates and not to any individual enantiomer. There were, however, express references to the enantiomers in both the body of the specification and in the claims of each of the prior art patents. Those express references, particularly in the Canadian

prior art patent, led the primary judge to conclude that each of the prior art patents '*plainly carry the claim that the enantiomers are within the compounds disclosed*', separate from the racemate and from each other. The fact that the efficacy or toxicity of the enantiomers could not have been known prior to obtaining the enantiomers was not to the point and did not affect that disclosure. His Honour concluded that the invention disclosed and claimed by the French prior art patent '*necessarily carried the implication of a direction, recommendation or suggestion*' to obtain PCR 4099 and its individual enantiomers. His Honour noted that the invention of the French and corresponding prior art patents was not described by reference to a particular result as to efficacy or toxicity and the claims were not so limited. The formula of the racemate was expressly disclosed as having the claimed advantage and the same claim was made in relation to each enantiomer. His Honour rejected the evidence of the Sanofi witnesses that the claims of the prior art patents did not encompass each of the separated single enantiomers of the derivatives.

91 The primary judge gave detailed consideration to the authorities on the requirement for "an enabling disclosure". His Honour's summary was, in part, set out in *H Lundbeck A/S v Alphapharm Pty Ltd* (2009) 81 IPR 228 at [169]. His Honour did not accept that, for the purposes of anticipation of a product claim, there was a separate requirement that the disclosure be "enabling".

92 The primary judge also considered whether the Patent describing and claiming the d-enantiomer could be categorised as a "selection patent". Despite expressing reservations about the concept of selection patents, his Honour concluded that the Patent did not fulfil the requirements for a selection patent as set out in *IG Farbenindustrie* at 322-323 and as restated, in part, in *Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC* (2008) 77 IPR 449 at [105]. His Honour held that, even if there were a special category of "selection patents", the principles did not apply in this case, where the enantiomers were expressly disclosed and claimed in the prior art patents and in the context of the same relevant activity as the racemate, blood-platelet aggregation inhibition. Accordingly, the advantages of the d-enantiomer are not different in kind from those described and predicted in the prior art patents and the claimed activity is not '*out of the range of results predictable from the tests done on the examples in the earlier specification*'.

93 The primary judge found that:

- Claims 1, 10 and 11 are not novel over the prior art patents.
- Claims 1, 10 and 11 cannot be defended from anticipation as valid selections.
- There is no disclosure of the precise formula of claim 3 in the prior art patents. There is not a clear description of the salt of claim 3. There are no clear instructions to do or make that particular salt. The attack on novelty in

relation to claim 3 fails. The same reasoning would apply to claims 2, 4 and 5.

94 His Honour did not deal with the inclusion within claim 1 of the pharmaceutically acceptable salts of the d-enantiomer.

Sanofi's submissions on the novelty of claim 1

95 Sanofi submits that the primary judge incorrectly applied the law. Sanofi submits that the principles stated in *Hill v Evans* (1862) 1A IPR 1 apply to claims to a process and also to claims to a product. It is clear from the authorities, Sanofi says, that to anticipate a claimed invention, a prior paper disclosure that does not itself clearly show the production of the claimed invention must inevitably result in the skilled addressee arriving at the claimed invention.

96 Sanofi submits that the requirement is for clear disclosure and that, in relation to the prior art patents, where:

a. the patentee had not made the d-enantiomer of PCR 4099; and

b. the patentee did not show a method of producing it by resolving it;

c. but it is possible that the skilled addressee, using known methods, might be able to make it;

there is no clear disclosure of the d-enantiomer in the prior art patents.

97 Further, if a requirement for a novelty-defeating prior publication is enablement, those same matters, Sanofi says, show that there was no such enablement.

98 There can be no dispute that each of the prior art patents not only disclosed the racemate but also specifically referred to and claimed the individual enantiomers. Sanofi says that the primary judge erred in his approach which did not, it submits, adequately address what the skilled addressee would understand to have been disclosed in the prior art patents.

99 Sanofi's submission is that, in the context of a product claim, a prior publication is not novelty defeating unless the skilled addressee would have made the claimed invention from the prior disclosure. Sanofi relies for this conclusion on *Hill v Evans* and subsequent authorities and the notion that, to anticipate, the prior disclosure must inevitably result in the skilled addressee arriving at the claimed invention. However, *Hill v Evans* was, in that context, discussing the prior description of a process or method.

100 The relevant question is whether any of the prior art patents describe the claimed invention with sufficient clarity to the skilled reader (*Bristol-Myers Squibb* at [67]).

101 Sanofi submits that, had a claim been made in the prior art patents for the efficacy of the enantiomers separately, the claim would properly be described as a "bare claim" without any support in the specification. It says that the addressee of the Canadian prior art patent (and

the other prior art patents) would know that one cannot know which of the enantiomers has the desired activity without making and testing them. It says that further discovery was needed before it was known that the d-enantiomer should be chosen and '*before the claimed invention* [was] *obtained*'. Further, apparently ignoring the direction to obtain the enantiomers "if desired", it says that there are no clear or unmistakable directions to make the d-enantiomer and that, even if there were, no one had previously separated the enantiomers of PCR 4099. Although diastereomeric salt formation and asymmetric synthesis were routine methods applied to obtaining enantiomers from a racemate, Sanofi says that those methods were not assured to work on PCR 4099.

102 It is worth noting that the primary judge did not accept the evidence of Sanofi's witness, Mr Badorc, as to the difficulties encountered in the separation process of diastereomeric salt formation. In that regard, his Honour's findings differed from those in some other courts, for example in Canada and the US. The primary judge concluded that the work of Mr Badorc did not involve any inventive step and that the steps that he took were typical of the trial and error that was necessarily involved with the use of the technique of diastereomeric salt formation.

Consideration of the novelty of claim 1

103 It is to be recalled that the invention claimed in claim 1 of the Patent is to a product alone: the

d-enantiomer of PCR 4099 and to its pharmaceutically acceptable salts, unlimited as to use or purpose, or level of activity or toxicity, or as a product of a process. The question whether a prior publication anticipates a subsequent claimed invention depends upon the quality of the disclosure in that prior publication, as assessed through the eyes of the skilled addressee. Apotex accepts that a disclosure will not be sufficiently clear if it is necessary to supplement the disclosure by means of experiments or other sources of information in order to perceive the disclosure. However, that is not the same as accepting that, where there has been disclosure of a product, the method of producing that product must also be disclosed.

104 Some of the same issues concerning novelty arose in *Lundbeck*, a case which also involved a claim to the (+)-enantiomer of a racemate. From the consideration in *Lundbeck*, the following is apposite to the consideration of anticipation by the prior art patents in this case:

- Where the prior publication discloses exactly what is claimed, there is anticipation (*Lundbeck* at [180]).

- There is anticipation if the skilled addressee would add missing information to what is disclosed in the prior art as a matter of course and without the application of inventive ingenuity or undue experimentation (at [181]). A disclosure is sufficient if it enables the skilled addressee, in the ordinary course and without invention, to add what is

missing in the prior publication to obtain the claimed invention (at [183]).

- If the prior art discloses the very subject matter of the invention, the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work (at [189]). If the disclosure is of an invention which, if performed, would infringe the patent, there is anticipation.

- The question is whether the disclosure is sufficient to enable the skilled addressee to perceive, understand and, where appropriate, apply the prior disclosure necessarily, but within the ordinary limits of trial and error, to obtain the invention (at [190]).

105 In *Lundbeck*, there was no reference to the enantiomers in the prior patent for the racemate. The prior patent disclosing and claiming the racemate did not render the claims to an individual enantiomer invalid for lack of novelty. A prior art article, the Smith article, made reference to the R and S enantiomers of the racemate but not to the (+) and (–) (or d and l) enantiomers. There is no correlation between the R and S designations and the (+) and (–) designations. There was no anticipation in circumstances where the reference to the R and S enantiomers and the knowledge that a racemic mixture contains enantiomers were not sufficient to disclose the (+) and (-) enantiomers and where the preparation of the (+)-enantiomer involved an inventive step or undue experimentation.

106 In this case, there was a disclosure of the enantiomers in the prior art patents. Those enantiomers were not only described, they were also claimed. Thus there was a clear direction to the skilled reader to prepare the enantiomers and in addition, but not necessarily, it was made clear that such enantiomers were, or were likely to be, useful for the desired purpose. The primary judge was not in error in concluding that the prior art patents disclosed the enantiomers as part of the invention and as compounds predicted to have the beneficial qualities of the compounds exemplified. If his Honour were correct in his conclusion that the skilled reader would understand to separate the enantiomers and would know the methods to apply, and that the preparation of the d-enantiomer was routine and involved no inventive step, it is hard to see how his Honour erred in concluding that there had been disclosure of the d-enantiomer to the skilled addressee and that a claim to the d-enantiomer had been anticipated (*Ranbaxy*).

107 Sanofi emphasises that it was not possible without separation and testing of the enantiomers to predict with certainty their activity or toxicity, or which enantiomer should be chosen and which excluded for the purposes of the desired activity. Further, it says, while a range of techniques for obtaining enantiomers from a racemate were well-known prior to the priority date, choices were involved in the well-known method of diastereomeric salt formation and trial and error experimentation carried no guarantee of success.

108 Sanofi's submissions seem to suggest that unless the claimed compound was actually made and the making of it described in the prior publication, there could be no anticipation. We do not accept that submission. Sanofi appears to submit that it would have been necessary for the prior publication to describe, or for the evidence to establish, a prior resolution of PCR 4099 or, at least, of a compound of the general formula as claimed in each of the prior art patents. That is, Sanofi's submissions are to the effect that it would be necessary for a prior publication, in every case, to set out the method of preparation, no matter how routine, and presumably the detailed methodology of each step taken in the preparative process. That cannot be correct.

109 That is not to say that the disclosure of a racemate will, by itself, anticipate a later claim to an enantiomer of that racemate. It may do so or it may not. That will depend on the evidence of the skilled addressee and the particular context.

110 Sanofi draws in aid the fact that each of the prior art patents suggests that PCR 4099 would have the desirable activity and lack of toxicity so that, despite the references to the enantiomers, there was a "teaching away" of the undertaking of the preparation of the enantiomers. For the reasons in *Lundbeck*, this is not an answer to the claim of lack of novelty. In any event, there was a teaching that the racemate was useful but there was also a teaching that the individual enantiomers would be expected to display activity.

Selection patents

111 The primary judge expressed some doubt about the applicability in Australia of the concept of selection patents but proceeded to consider the criteria for such a patent as set out in *IG Farbenindustrie* and as referred to by the Full Court in *Ranbaxy* in the context of a consideration of false suggestion. In *Ranbaxy*, IP Australia considered the patentee's submissions to be that the claimed invention could be considered a selection.

112 His Honour said at [79] that, in his view and after considering various authorities, the concept does not recognise a special class of patents but '*is a convenient shorthand to pick up the relevant principles concerning anticipation*'.

113 As summarised by the Full Court in *Ranbaxy* at [105], in order to advance the proposition that the claimed invention constitutes a "selection" such that it is not anticipated by the disclosure of a class of compounds of which it is a member, the claimed member has to satisfy certain requirements:

- There must be some substantial advantage to be secured by the use of the selected members;
- The whole of the selected members must possess the advantage in question;
- The selection must be in respect of a quality of a special character, which can fairly be said to be peculiar to the group; and

- The advantage possessed by the selected members must be clearly disclosed in the specification.

114 The primary judge found that, if a selection were available, it could be satisfied by the selection of the d-enantiomer from the class comprising the d-enantiomer, the l-enantiomer and the racemate. His Honour concluded that there is a substantial advantage to be secured by the use of the d-enantiomer as compared with the use of either the racemic mixture or the l-enantiomer. That advantage is that the d-enantiomer is better tolerated or less toxic and as effective as the racemate at a lesser concentration. Clearly, as his Honour said, the second and fourth criteria are also satisfied.

115 However, the primary judge concluded that the third criterion was not satisfied, as the French and corresponding prior art patents described the advantages very generally, the claims were not limited to any particular result and it was not claimed that each compound within the class described would have equal qualities. That is, the qualities of the d-enantiomer were not of a special character in exerting an effect on blood-platelet aggregation, Rather, the differences exhibited in activity and toxicity were quantitative differences. Such quantitative differences were envisaged in the prior art patents. His Honour said that the results for the d-enantiomer were by no means out of the range of results predictable from the tests done on the examples in the earlier specifications. His Honour also found, and it is not challenged, that it was part of the

common general knowledge that there was a range of potential difference in activity between enantiomers and that one enantiomer may have all of the activity and the other none. Further, it was not unusual for one enantiomer to display most of the activity and the other little (at [35(4)(ii)]). That is, the advantages of the characteristics of the d-enantiomer were not unexpected (at [86]-[87]). No other special advantages are described in the Patent.

116 Sanofi supports the primary judge's characterisation at [81] of the class from which the selection was made as the racemate, the selected enantiomer and the non-selected enantiomer. Sanofi observes that his Honour equated the requirement of a "quality of a special character" with "unexpectedness" and submits that the characteristics of the d-enantiomer were unexpected. It says that the fact that one enantiomer of the class exhibits all of the activity and the other none, and that the active enantiomer is well-tolerated, could not have been predicted where there is a range of potential difference in activity and toxicity. As such, it submits that the result was unexpected, as were certain additional advantages, such as the fact that the d-enantiomer does not undergo racemisation or interconversion in the body.

117 It is not necessary to decide whether or not there is a special category of "selection patents" which, if they satisfy the test in *IG Farbenindustrie*, may overcome a claim of lack of novelty. Any such category was not, in our view, intended to exclude from the requirement of

novelty a compound (here, the d-enantiomer) that was previously disclosed and claimed as one of a class of inventive compounds that demonstrated, or were predicted to demonstrate, particular activity and tolerance at various levels, and the compound was then shown to demonstrate that same activity at a high level, with high tolerance.

118 Assuming for the purposes of this appeal, without deciding, that there is a category of "selection patents", the d-enantiomer is not novel over the prior art patents.

The pharmaceutically acceptable salts of the d-enantiomer

119 As has been noted, claim 1 of the Patent is to the d-enantiomer of PCR 4099 and its pharmaceutically acceptable salts. Claim 3 is to a specific salt of the d-enantiomer, the hydrogen sulphate salt. Claims 2, 4 and 5 are to other specific salts.

120 Apotex relies on the following reference in the Canadian prior art patent as an anticipation ('the Expression'):

> . . . then the derivative sought is obtained, which is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action; . . .
>
> (Emphasis added).

121 The primary judge was of the view that the prior art patents most naturally refer to the salts of the racemate rather than of the enantiomers. We agree.

122 His Honour also said that, even if the salification referred to the enantiomers, there was a choice of acid to be made, so that there was not the necessary disclosure to anticipate a claim to a particular salt, either by providing a clear description of the salt (for example, of claim 3) or by providing clear instructions to do or make that particular salt. Sanofi points to the evidence that, while the method of preparation of the salts may be standard, there was a choice to be made in relation to which salt of the d-enantiomer to make. That process, it says, involved trial and error, and a choice in terms of acid, to produce a salt with appropriate properties such as being able to crystallise easily, not being hygroscopic and being sufficiently water-soluble. Consequently, the skilled reader could not predict that a particular acid would result in a pharmaceutically acceptable salt of the d-enantiomer.

Claim 1 and the pharmaceutically acceptable salts of the d-enantiomer

123 Claim I of the patent is not only to the d-enantiomer of PCR 4099 but also to its pharmaceutically acceptable salts. The primary judge did not consider the latter part of claim 1. The claim to the d-enantiomer is not novel, being anticipated by the prior art patents.

124 Using the Canadian prior art patent to examine what is said in the prior art patents concerning the pharmaceutical salts of the compounds of the invention:

- The specification states:

  > These compounds include an asymmetrical carbon which may exist in the form of 2 enantiomers. The invention also concerns each of the enantiomers and their mixture.
  >
  > The invention also includes the addition salts with pharmaceutically acceptable mineral or organic acids . . .

- The examples are of salts of the racemic mixtures, for example, hydrochloride and bisulphate (ie. hydrogen sulphate) salts.

- All of the pharmacological and toxicological results presented for the salts are for salts of racemates.

- Claim 1 is to a process for the preparation of derivatives of the given general formula (formula (I)) and their addition salts with pharmaceutically acceptable mineral or organic acids or with mineral bases, as well as the two enantiomers or their mixture of the compounds of formula (I). The claim does not link the enantiomers to the addition salts.

- Claim 1 then continues with the Expression. The Expression (or an expression relevantly the same) appears three times in the claim. The Expression does not link the enantiomers to the addition salts.

- Claim 14 refers to the enantiomers but that reference does not link the enantiomers to addition salts: '*Derivatives of general formula*

> *(I) . . . and their addition salts with pharmaceutically acceptable mineral or organic acids . . . or with mineral bases . . . ; as well as the 2 enantiomers or their mixture of these compounds of formula (I)*'.

125 We do not accept Apotex's or Spirit's submission that the references, in context, are to the pharmaceutical salts of the enantiomers.

126 Turning to the Australian prior art patent and bearing in mind that the derivatives of formula (I) were racemates, the specification contains the general statement:

> Thus, the invention also relates to a therapeutic composition having in particular an inhibiting action on blood-platelet aggregation and anti-thrombotic action, wherein the active ingredient is a derivative of the formula (I) or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid . . . or with a mineral base . . .
>
> (Emphasis added).

127 Claim 14 of the Australian prior art patent claims a therapeutic composition containing as active ingredient a derivative of formula (I) as claimed in claim 1, '*or an addition salt* ***thereof*** *with a pharmaceutically acceptable mineral or organic acid or with mineral bases,* ***as well as*** *one of the two enantiomers or their mixture*' (emphasis added).

128 These are not disclosures of the pharmaceutical salts of the enantiomers. The disclosures

of the French and US prior art patents are relevantly in the same terms.

129 It is clearly stated in each of the prior art patents that the invention therein described relates not only to the racemic mixture of the two enantiomers but also to each enantiomer of, *inter alia*, PCR 4099. For example, the Australian prior art patent states that '[t]*he invention relates both to each enantiomer and their mixture*'. However, the disclosures of addition salts and pharmaceutically acceptable salts are of the racemates. That reading of the prior art patents is consistent with evidence from skilled addressees. The pharmacological and toxicological tests were also of the salts of the racemate.

130 The specification of the Patent states that the invention which relates to the d-enantiomer of PCR 4099 relates also to the addition salts of the d-enantiomer with pharmaceutically acceptable mineral or organic acids. The Patent also makes reference to the difficulty of purifying the d-enantiomer, which is an oil, and states that it is preferable to use crystalline products which can usually be purified by recrystallisation. Sanofi concedes that there was nothing inventive in the method of salt formation in the Patent and that it was generally the same technique as described in the Canadian prior art patent. However, the specification says that the purification of at least some salts proved to be difficult and that some had undesirable properties (such as being hygroscopic). While the salts are prepared '*in a standard manner by the action of the corresponding acid on the base in solution in a solvent*', it

required finding salts which crystallise easily, are not hygroscopic and are sufficiently water-soluble.

131 The pharmaceutically acceptable salts of the d-enantiomer were not anticipated and are novel over the prior art patents.

Conclusion on the novelty of claim 1 of the Patent

132 The enantiomers of PCR 4099 were disclosed and claimed in each of the prior art patents. Further, the prior art patents each contained a direction, recommendation or suggestion which, if followed, would result in the d-enantiomer of PCR 4099. A range of techniques for obtaining enantiomers from a racemate was known and commonly applied prior to 1987. If his Honour were correct in his conclusion that the process used to obtain the enantiomers of PCR 4099 was obvious then, in our view, this further constituted each of the prior art patents as a novelty-defeating disclosure of the d-enantiomer. However, the pharmaceutically acceptable salts of the d-enantiomer were not disclosed in any of the prior art patents. The only salts disclosed were those of the racemate. Accordingly, the pharmaceutically acceptable salts of the d-enantiomer were not anticipated and are novel over the prior art patents.

Claims 2 to 5 of the Patent

The findings of the primary judge on the novelty of claims 2 to 5

133 The primary judge found that the invention as claimed in each of claims 2 to 5 was not anticipated, not having been disclosed in the prior art patents, on the basis that:

- There was no disclosure of the precise formula of claims 2 to 5;
- The specifications of the prior art patents most naturally refer to salts of the racemate rather than of the enantiomers;
- There is a choice of acid to be made in relation to making salts of the d-enantiomer;
- There was not a clear description of the salts described in claims 2 to 5; and
- There were no clear instructions to make the particular salts of claims 2 to 5.

134 The prior art patents refer to and therefore direct the reader to mineral acids and organic acids. The three salts of claims 2 to 4 of the Patent, hydrochloride, hydrogen sulphate and hydrobromide, are all mineral salts. The salt of claim 6, taurocholate, is an organic salt. However, while there were examples of similar salts of the racemates provided, this was not sufficient to constitute a direction that would inevitably lead to the subject matter of claims 2 to 5, particularly in circumstances where many other salts could have been chosen and used.

Apotex's and Spirit's submissions on the novelty of claims 2 to 5

135 Apotex and Spirit submit that the prior art patents disclose the enantiomers and the addition salts of the enantiomers with pharmaceutically acceptable mineral or organic acids. To the extent that this submission is based on the Expression and on claims 1 and 14 of the Canadian prior art patent, the salts of the enantiomers are not thereby disclosed. Apotex then submits that, even if the salts as described and exemplified in the prior art patents are of the racemates, including PCR 4099, and not of the enantiomers, the examples are said to be non-limiting and that the mineral acids used in the examples are commonly used pharmaceutically acceptable mineral acids, Although the only express combination of PCR 4099 is with hydrochloric acid in the prior art patents, Apotex submits that all that is required of the skilled addressee '*is merely to realise that the addition salts disclosed include PCR 4099 . . . and its enantiomers, with another common mineral acid, sulfuric acid*', which does not, Apotex says, require inventive ingenuity or an inventive step. The same would apply to the combination of PCR 4099 and its enantiomers with hydrobromic and taurocholic acids. The latter acid is not referred to in any of the prior art patents.

Consideration of the novelty of claims 2 to 5

136 There is no direction in the prior art patents, let alone a direction that would inevitably or without undue experimentation lead to the

claimed invention of claims 2 to 5. The skilled reader would be required to take from the prior art patents the disclosure that he or she should make the pharmaceutically acceptable salts of the d-enantiomer of PCR 4099, to know the method to apply to make a salt of the d-enantiomer of that derivative and to choose the specific salts out of the possible range of mineral and organic acids. A hydrogen sulphate salt and a hydrobromide salt of derivatives other than PCR 4099 are disclosed in the prior art patents. However, in the case of claims 3 and 4 of the Patent, the skilled reader would have to know to choose a salt not exemplified in the prior art patents for PCR 4099. No salt using taurocholic acid is exemplified in the prior art patents. This is not a case where, as Apotex submits, the skilled reader has "merely" to follow the "teaching" of the prior art patents. There is no instruction or direction or teaching in any of those patents in relation to the salts of the d-enantiomer as claimed in claims 2 to 5.

137 The requirement for lack of novelty is that the prior publication anticipate or disclose the claimed invention, not that it renders it obvious to the skilled reader to apply or try to apply what is disclosed for one compound to another. It is not a case where the examples demonstrate that a technique is applicable to some members of a class of compounds, being enantiomers of the derivatives of formula (I), and can then be said to be disclosed as applicable to the whole of the class. The prior art patents do not say to make, nor do they exemplify, the salts of the enantiomers. The direction is limited to the racemic

mixtures. There is no clear description of, or clear instructions to make, something that would infringe the subsequent claims to the salts of the enantiomers. Even if there were a direction to make a salt of the enantiomers, the direction could be carried out in a way that would not result in infringement of claims 2, 3, 4 or 5 and that does not constitute anticipation (*General Tire & Rubber Company v Firestone Tyre and Rubber Company Ltd* (1971) 1A IPR 121; *Olin Corporation v Super Cartridge Co Pty Ltd* (1977) 180 CLR 236; *Lundbeck* at [169] and [173]).

138 As the primary judge said at [89], there is not, in any of the prior art patents, a clear description of the salts described in claim 3 (or claims 2 or 4 or 5) or clear instructions to do or make that particular salt. The prior art patents do specify three of the specific salts as salts of a racemate. That is not sufficient to constitute an anticipation of the choice of salt of one of the enantiomers of PCR 4099. There was no direction to salify the d-enantiomer of PCR 4099, let alone to make the particular salts of claims 2 to 5.

139 Apotex says that for the prior art patents to exclude the salts of the enantiomers offends against common sense. We are not satisfied that that is the case. The prior art patents were drafted by the patentee, presumably carefully. The enantiomers were not described as having been obtained but they were disclosed and claimed. The patentee may have had good reason for not describing or claiming the application of a process to a product not yet produced.

140 Apotex has not demonstrated that the primary judge was in error in concluding that claims 2 to 5 were novel.

Claims 10 and 11 of the Patent

141 The primary judge said that his conclusion as to claim 1 "also affects" claims 10 and 11. Those claims are to pharmaceutical compositions comprising as active ingredient one compound of one of the claims 1 to 5.

142 Spirit points to the statement in the Canadian prior art patent, in general terms, that the drug of the invention may be orally administered in the form of tablets, coated tablets, capsules, drops, granules or syrup and in a dose from 0.005g to 0.250g of a derivative of the invention, the daily dosage regimen varying within the range from 0.005g to 1.00g of active ingredient. Examples disclose pharmaceutically acceptable carriers within the description in claim 10 of the Patent and doses within the range of claim 11 of the Patent. The examples of the formulations of five of the derivatives, which comprise the active ingredient with a pharmaceutically acceptable carrier, are stated to be "non-limiting".

143 The Canadian prior art patent discloses, generally, "the drug of the invention", which includes the d-enantiomer of PCR 4099, with pharmaceutically acceptable carriers, thus anticipating claim 10 of the Patent which claims a pharmaceutical composition comprising as active ingredient one compound of one of claims 1 to 5 in that form.

144 Claim 11 of the Patent is to a composition according to claim 10, comprising unit doses containing from 0.001g to 0.100g of active ingredient. The non-limiting examples of the formulation of the Canadian prior art patent contain the active ingredient in a range that intersects with the range claimed in claim 11. The active ingredient of the Canadian prior art patent includes the enantiomers of PCR 4099. This anticipates claim 11 of the Patent.

OBVIOUSNESS

The starting point for the assessment of obviousness

145 It is not in dispute that the obviousness of the claims of the Patent is to be assessed under s 100(1)(e) of the 1952 Act. That is, whether '*the invention so far as claimed in any claim of the complete specification . . . was obvious and did not involve an inventive step having regard to what was known or used in Australia on or before the priority date of that claim*'.

146 In *Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* (2007) 235 CLR 173, the High Court restated, shortly, the history of the introduction of obviousness as a ground of invalidity and the distinction between novelty and obviousness. The Court also emphasised the balance of policy considerations in patent law, to encourage and reward inventors without impeding advances and improvements by skilled, non-inventive persons. The High Court reaffirmed at [51]-[56] a number of the principles to

be applied to a determination of obviousness including, relevantly:

- "Obvious" means "very plain".
- The question whether an invention is obvious is a question of fact.
- The question of inventive step is one of degree. Ingenuity is relative, depending on relevant states of common general knowledge.
- The question is always *'is the step taken over the prior art an "obvious step" or "an inventive step"'*.
- There is no distinction between obviousness and a lack of inventive step.
- There must be "some difficulty overcome, some barrier crossed".
- The essential question to be posed when considering obviousness under the 1952 Act was that set out in *Wellcome Foundation Limited v VR Laboratories (Aust) Proprietary Limited* (1981) 148 CLR 262: the question of obviousness involves asking whether **the invention** would have been obvious to a non-inventive worker in the field, equipped with the common general knowledge in that field, without regard to documents in existence but not part of common general knowledge.
- Common general knowledge, as explained in *Minnesota Mining and Manufacturing Company v Beiersdorf (Australia) Limited* (1980)

144 CLR 253 at 292, is the background knowledge and experience which is available to all in the trade in considering the making of new products, or the making of improvements in old.

- For the purpose of determining inventiveness, prior disclosures which were not part of common general knowledge are excluded from consideration.

147 The High Court in *Lockwood (No 2)* also made some general observations regarding the patentability of ideas:

- An invention may, and usually does, involve three processes:
  - The definition of the problem to be solved or the difficulties to be overcome;
  - The choice of the general principle to be applied in solving this problem or overcoming these difficulties; and
  - The choice of the particular means used.

  Merit in any one of these stages, or in the whole combined, may support the invention.
- There is a distinction between the idea or concept or principle informing an invention and the means of carrying it out or embodying it in a manner of new manufacture.
- Invention may lie in the idea of taking the step in question. An inventive step can be having an insight rather than a mere development and application of existing ideas.

148 Apotex claims that all of the claims in dispute are obvious but accepts that this depends on the starting point for that assessment. Apotex contends that the correct starting point is the racemic mixture, PCR 4099. As neither that compound nor any of the prior art patents were part of common general knowledge in Australia at the priority date, Apotex accepts that if common general knowledge is the starting point, the claims are not obvious. Sanofi contends that the correct starting point is the common general knowledge of the hypothetical non-inventive worker in the field as at the priority date of the Patent.

149 There is no dispute that '*what was known or used in Australia*' (s 100(1)(e) of the 1952 Act) means the common general knowledge in the relevant field (*Minnesota Mining*). If PCR 4099 is the correct starting point, Apotex and Spirit rely on the unchallenged findings of the primary judge as to the content of common general knowledge in support of their assertion that the subject matter of the claims was obvious.

150 Apotex submits that the primary judge erred in applying different starting points for the purpose of assessing the obviousness of different claims. In any event, the key issue is the correct starting point.

151 Obviousness and inventive step are antitheses. What is obvious does not involve an inventive step and vice versa (*Lockwood (No 2)* at [52]).

152 Section 100(1)(e) makes it clear that the question to be addressed is whether **the invention**, so far as claimed in the particular claim, is obvious and does not involve an inventive step. That requires a determination of the invention, as described in the specification. What is claimed may then equate with, or be less than the totality of or scope of, the invention. The specification of the Patent makes it clear that the selection of PCR 4099 as the racemate to be resolved formed no part of this invention as described and claimed. From the primary judge's reasons, no such claim was made. It was the process of separation of the enantiomers of that mixture to obtain the enantiomers, and, in turn, the pharmaceutically acceptable salts of the d-enantiomer, that broadly, were the subject matter of the claims. The invention to be assessed for obviousness is ascertained from the patent and the obviousness or inventive step of the invention as claimed is then assessed by reference to common general knowledge in Australia at the priority date.

153 This analysis of the invention assists in determining the correct starting point for the application of the common general knowledge of the hypothetical person of skill in the art in order to decide whether the invention as claimed in the claims was obvious or involved an inventive step. The invention presupposes that the hypothetical worker was in possession of the racemate and the knowledge that it had platelet aggregation inhibiting activity. As the primary judge said, the desire to separate the enantiomers should be taken for granted. Knowledge of the kind of

activity was a prerequisite to testing the enantiomers for that activity which led to the asserted unexpected result that the l-enantiomer did not exhibit any such activity. However, the hypothetical skilled worker would not know the contents of the French prior art patent or, indeed, the other prior art patents, that were not part of common general knowledge.

154 The "problem/solution approach" yields the same result.

155 In *Wellcome*, Aickin J expressed the test for obviousness as:

> whether the hypothetical addressee faced with the same problem would have taken as a matter of routine whatever steps might have led from the prior art to the invention, whether they be the steps of the inventor or not.

156 *Minnesota Mining* at 292 talks of the '*process of applying such common general knowledge to the solution of a problem*'.

157 In *Aktiebolaget Hässle v Alphapharm Pty Limited* (2002) 212 CLR 411, the patentee accepted that the notional addressee is to be told the nature of the problem but is not provided with information not part of common general knowledge and obtainable only by testing. The majority, Gleeson CJ, Gaudron, Gummow and Hayne JJ, referred at [40] to what was said by Lord Hoffmann in *Biogen Inc v Medeva plc* (1996) 36 IPR 438:

> A proper statement of the inventive concept needs to include some express or implied reference to the problem which it required invention to overcome.

158 While their Honours apparently questioned the English (and European) approach of "problem and solution", they referred to the earlier acknowledgment by Buckley LJ in *Re Beecham Group Ltd's (Amoxycillin) Application* [1980] 97 RPC 261 to the solution of '*some recognised problem*' and the meeting of '*some recognised need*'. Their Honours also referred expressly to the consistory clause in the Hassle patent, which stated that the claimed invention was designed to obtain a pharmaceutical dosage form of omeprazole to answer the problems identified in the specification. Omeprazole itself was not part of common general knowledge. Their Honours stated that it was the interaction between the combination of integers of the formulation that was the essential requirement for the presence of an inventive step.

159 The High Court in *Lockwood (No 2)* re-stated or clarified its position on the "problem and solution" approach and, again, cited the reference of Lord Hoffmann in *Biogen Inc* to the problem which it required invention to overcome. The High Court now makes it apparent that it does not reject such an approach, where appropriate. The question of obviousness is not confined to a problem/solution approach. It may not be appropriate or sufficient where, for example, no skilled person in the art had thought of a general

idea or general method of solving a known difficulty with respect to a known product or where the appreciation that there was a problem with a known product was itself part of the inventive concept. As the High Court said at [105], while not every invention constitutes a solution to a problem, it is commonplace so to describe an invention where it is appropriate to do so. However, admissions about a problem in a specification need to be weighed with evidence of the perception of any problem by the person of skill in the relevant art, before exposure to the solution contained in the invention.

160 The problem addressed in the Patent is the resolution of the enantiomers of PCR 4099. The problem described is the difficulty of purifying the d-enantiomer and of obtaining suitable salts. Accordingly, the hypothetical skilled worker armed with common general knowledge would have that racemic mixture as the starting point. The question is then whether, from that starting point, the claimed invention was obvious; whether there was an inventive step, as assessed by reference to the common general knowledge, in resolving the enantiomers and obtaining pharmaceutically acceptable salts of the d-enantiomer. It should be emphasised that the base line or starting point may itself be part of the inventive step or inventive process but that is not the case here. The selection of PCR 4099 for resolution was not claimed to be inventive.

161 The French prior art patent as referred to in the specification of the Patent does assist in understanding the starting point and context of

the invention described and claimed. However, it is clear, as the primary judge accepted, that the reference to the French prior art patent in the specification of the Patent does not make that patent part of common general knowledge. It does not make that patent available to tell the notional skilled addressee the results of the testing of formulations of PCR 4099.

162 As the Full Court said in *Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* (2008) 78 IPR 20, close attention should be given to the terms of the individual specification to understand what admissions are made and also to understand the invention. In *Insta*, previous patents of the same inventor were cited but this did not constitute an admission that the inventions the subject of those patents had become part of common general knowledge. Rather, the specification described the inventor's own inventive journey (at [84]) and his own familiarity with the inventions the subject of earlier US patents (at [104]). Importantly, the claim in that case was to an entire structure or construction, which included the subject matter of those earlier US patents with additional features described in the specification. The invention was not limited to the introduction of new features into an existing structure (at [92]).

163 Sanofi chose to file a separate patent for the claimed invention, the d-enantiomer, its pharmaceutically acceptable salts and the process for obtaining that enantiomer from the racemic mixture of PCR 4099. The invention of the Patent starts with a biologically active racemate.

Common general knowledge

164 The primary judge made a number of findings concerning common general knowledge as at the priority date of the Patent in relation to:

- The fundamental principles of stereochemistry;
- Methods for obtaining individual enantiomers from a racemate;
- The formation of salts of stereochemical compounds for pharmaceutical purposes; and
- The biological/pharmacological activity and toxicity of stereochemical compounds and the ability to predict same.

165 There is no dispute with his Honour's findings at [35] and [36] as indicative of the state of common general knowledge in the relevant field in Australia as at the priority date of the Patent in relation to each of these four issues, which would also be matters understood by and known to the skilled addresses of the Patent.

166 At [35] of his reasons the primary judge distilled from the evidence of the expert witnesses the state of common general knowledge in the relevant field in Australia by 1987:

> (1) The principles of stereochemistry were well known prior to 1987. They, as well as information concerning techniques for obtaining enantiomers, were taught to undergraduate students, and university students more generally, from the 1960s through to 1987. There have been no

significant changes in the science of stereochemistry since 1987, though certain advances have been made in the understanding and application of certain techniques for obtaining enantiomers, asymmetric synthesis being an example

(2) (i) A range of techniques for obtaining enantiomers from a racemate was well known prior to 1987. Information concerning those techniques, and in particular diastereomeric salt formation, were taught to undergraduate students from the 1960s, though this may not always have involved practical experimentation. Asymmetric synthesis was also a known technique, though query whether it was to be understood as a "separation" technique.

(ii) Prior to 1987, diastereomeric salt formation was a well developed method, which was straightforward and routine, though involving choices. Those choices included choices of chiral resolving agent (acid or base as required) and solvent. The variety of choices in that regard, as well as certain other factors, meant that the process may well involve trial and error experimentation carrying no guarantee of success. That was, however, not such as to take the process beyond routine experimentation, including

in respect of parallel experimentation. Though a choice certainly existed in the drug development process as to whether to obtain enantiomers by diastereomeric salt formation or, say, asymmetric synthesis instead, or indeed simply to undertake a wider structure-activity study in the relevant class of compounds, diastereomeric salt formation was certainly a prominent, widely used and well developed technique prior to 1987. It is clear that many would have elected to use that technique as a first step, though there was obvious disagreement on that point. Though not without certain difficulties, the process had been known and reported to yield results, though not necessarily in relation to thienopyridine compounds.

(iii) As to the resolving acid or base, and solvent, there were clearly choices to be made in this regard. Guidance could be gained from the literature, though principally, it would appear, where similar compounds had already been resolved. Lists of standard chiral acids and amines were also available. Camphor-10-sulfonic acid was known as a chiral resolving agent prior to 1987 and its use was not new. Its commercial availability in both enantiomeric

forms was perhaps not certain, though it was possible to prepare a chiral form of the acid. Acetone was a well known and commonly used solvent prior to 1987. Further variables such as the temperature at which the experiment was conducted, the sealing and shape of the reaction vessel, the concentration of racemate to reagent and solvent respectively, the amount of solvent present and the room temperature, were variables to be dealt with as part of the normal experimentation process. As Apotex alluded to in its submissions, details as to those variables did not appear to warrant particular focus in the patent in suit.

(iv) The time that might be expected to elapse before obtaining a yield from the diastereomeric salt formation process, was a matter of some difference of opinion. What appears to emerge is that there is no fixed likely duration for such a process and, indeed, no ability to predict with certainty whether one will be successful. The process may involve immediate success (most likely meaning days) or may be drawn out over weeks. Months or years would not be expected. The process may also be without success. The process involves trial and error and may

require perseverance. Yields may be obtained that are sufficient for analysis of the activity of an enantiomer.

(3) The formation of pharmaceutically acceptable salts of both racemates and enantiomers, including those in the form of an oil, was a common process prior to 1987, the techniques for which were known. There was a choice to be made in relation to which salt would be made, that process involving trial and error, and hence a choice in terms of acid. Hydrochloric and sulfuric acids were, however, common laboratory acids and were used to make pharmaceutical salts prior to 1987.

(4) (i) It was well understood prior to 1987 that enantiomers can exhibit different biological activity and toxicity. The thalidomide example had clearly provided a cautionary tale in this regard. It was not possible without separation and testing to predict with certainty the activity or toxicity of an enantiomer. Some prediction might be made based on knowledge of the intended receptor or the properties of salt of the relevant racemate, but that knowledge, where it was available, still could not ensure certainty.

(ii) There was and is a range of potential difference in activity between enantiomers. At the extremes, activity may be the same, or one enantiomer might have all the activity and the other none. Those two extremes were, however, less likely and would have been less expected than a result in the intermediate range. It was not unusual for one enantiomer to display most of the activity and the other little. The difference between the activity of the racemate and that of the active enantiomer could be expected to be about two-fold, though that difference might increase where the inactive enantiomer served to inhibit the activity of the active enantiomer when both were present in the racemate.

(iii) The toxicity of an enantiomer is not related to its physiological activity.

167 At [113], the primary judge stated, and it is not disputed, that the acids relevant to claims 2 to 5, that is, hydrochloric acid, sulphuric acid, hydrobromic acid and taurocholic acid, were all conventional for the preparation of salts.

The inventive step

168 The question is then whether the skilled worker in the art would have taken as a matter of routine the steps leading from the starting

point to the invention; whether, in applying common general knowledge, that person would have resolved the enantiomers of the racemate to obtain the d-enantiomer and obtained the claimed salts and pharmaceutical compositions and, for the purposes of claim 6, by the process there set out.

169 The primary judge stated at [110] that the result which might be described as "unexpected" in light of the French prior art patent was not so much the desirable characteristics of the d-enantiomer, for which the activity was in the expected broad range, but the inactivity of the l-enantiomer. His Honour considered that the claimed inventive step in relation to the product claim was the unexpected inactivity of the l-enantiomer. An unexpected result obtained in the course of investigation can, his Honour accepted, provide subject matter for an invention in appropriate circumstances.

170 His Honour said that it was common general knowledge as at the priority date that one enantiomer may have all of the activity and concluded that the discovery of the inactivity of the l-enantiomer was not so unexpected as to amount to an inventive step. In coming to this conclusion, the primary judge seems to have taken account of the information in the French prior art patent referred to in the specification of the Patent because Sanofi described the d-enantiomer as a selection from the prior published PCR 4099 and its enantiomers.

171 However, turning to the pharmaceutically acceptable salts of claims 2 to 5, his Honour said that, as the salts of the d-enantiomer were novel without any consideration as selection patents, the starting point for the assessment of obviousness was neither PCR 4099 nor the individual enantiomers, but rather, the common general knowledge. Since PCR 4099 did not form part of that common general knowledge, the primary judge concluded that the salts of its enantiomers were not obvious and represented an inventive step.

172 His Honour concluded that the claimed processes (claims 6 to 9), which described the liberation of the d-enantiomer from PCR 4099 by diastereomeric salt formation, were invalid for want of inventive step. In the context of assessing the obviousness of claim 6, the primary judge stated that the desire to obtain the d-enantiomer of PCR 4099 from the racemic mixture is taken for granted. That is, his Honour concluded that the starting point for the assessment of the obviousness of the process claims was the racemate, PCR 4099.

Consideration of the obviousness of particular claims of the Patent

Claims 1, 10 and 11 of the Patent

173 As noted above, the primary judge concluded that, for claim 1, the asserted inventive step related to the discovery of the inactivity of the l-enantiomer. In light of the common general knowledge, his Honour did not accept that this

discovery was so unexpected as to amount to an inventive step. That finding has not been shown to be in error. The idea to separate the enantiomers of PCR 4099 was not claimed to be part of the invention and indeed the person whose idea it was to do so was not named as an inventor ([21(12)]).

174 Claim 1 extends to the pharmaceutically acceptable salts of the d-enantiomer, undifferentiated. The finding of the primary judge, which is unchallenged in the appeal, is that the formation of pharmaceutically acceptable salts of enantiomers, including those in the form of an oil, was a common process prior to 1987, the techniques for which were known. It was obvious to prepare such salts to investigate biological activity. While his Honour also found that there was a choice to be made in terms of the particular acid, the person of ordinary skill armed with the racemate would know to make a salt that was pharmaceutically acceptable. There was no inventive step in the pharmaceutical carriers of claim 10 or the specific dose ranges of claim 11.

175 It follows that the invention as claimed in claims 1, 10 and 11 was obvious.

Claims 2 to 5 of the Patent

176 The conversion of the d-enantiomer to the salts claimed in claims 2 to 5 is described in the Patent as being carried out '*in a standard manner*'. As the primary judge noted at [111], the specification does not claim any inventive step in

the method of obtaining the salts once the d-enantiomer was known. The primary judge said that, if the starting point were the single enantiomer, he would have held that each salt claimed was obvious. This was because it was known that a pharmaceutically acceptable salt was useful for administration of an active compound, it was known how to prepare such salts using known mineral or organic acids, the acids chosen were conventional and standard methods of preparation were known (at 113]).

177 The primary judge's finding as to the choice of individual salts is unchallenged. That is, there was a choice to be made as to which salt to make, a process involving trial and error and a choice of acid. However, as his Honour said ([35(3)]), hydrochloric and sulphuric acids were common laboratory acids and were used to make pharmaceutical salts prior to 1987. The primary judge also said at [113], and it is not challenged, that all of the acids used to make the salts of claims 2 to 5 – hydrochloric acid, sulphuric acid, hydrobromic acid and taurocholic acid – were conventional. Trial and error are normal, every-day parts of laboratory work and non-inventive laboratory experiments. That is what the hypothetical skilled worker in a laboratory does – if the outcomes of experiments were known, there would be little point in doing them. That is the nature of everyday, non-inventive, research. A non-inventive worker in the field, looking to make a pharmaceutically acceptable salt of the d-enantiomer would, on the evidence, choose an acid, such as those readily available and commonly and conventionally used, and apply

common processes and techniques to make it. That was obvious, in the sense that the non-inventive skilled worker would have been directly led to those particular salts. There was no inventive step involved.

178 On this basis there is no difference whether the starting point is the racemic mixture or the single enantiomer. From the findings of the primary judge as to the steps that would have been taken as a matter of routine by the non-inventive worker in the relevant field to obtain an enantiomer or the salts of an enantiomer, it follows that the salts of claims 2 to 5, being the hydrochloride, the hydrogen sulphate, the hydrobromide and the taurocholate, were obvious and the claims to them did not involve an inventive step.

Claims 6 to 9 of the Patent

179 The process claim is not for the decision to obtain the enantiomer but to the means of doing so. Sanofi submits that more than routine experimentation was required and that diastereomeric salt formation was not the only method for obtaining enantiomers. It cites evidence in support. However, his Honour found that the method used to obtain the d-enantiomer was well-known in the field in Australia at the priority date as a classic means of obtaining enantiomers of a racemate mixture, which was applied to a known compound and produced the desired result. There were no circumstances, his

Honour held, to make the choice of this known process inventive.

180 The primary judge also held that each of the additional integers of claims 7, 8 and 9 was well-known in the field in Australia at the priority date and was available as part of the ordinary process of trial and error. The chiral resolving agent used was known, its use was not new and the solvent was well-known and commonly used. These findings of fact were open to his Honour on the evidence.

181 Accordingly, the primary judge held claims 6, 7, 8 and 9 obvious.

182 It has not been demonstrated that the primary judge was in error in finding claims 6 to 9 obvious.

MANNER OF MANUFACTURE

183 The primary judge said at [118] that, in his opinion, it could not be suggested that the subject matter of the claims of the Patent is outside the meaning of the expression "a manner of manufacture" as discussed in *National Research Development Corporation v Commissioner of Patents* (1959) 102 CLR 252. The claims are for compounds and processes in a field of useful pharmacological application. His Honour also expressed the view at [121] that it cannot be said that the Patent claims an invention that is not new on the face of the specification of the Patent without regard to what may be described as external evidence. In that context, his Honour applied the

relevant factors, as far as he discerned them, in *NV Philips Gloeilampenfabrieken v Mirabella International Pty Limited* (1995) 183 CLR 655 and *Advanced Building Systems Pty Limited v Ramset Fasteners (Aust) Pty Limited* (1998) 194 CLR 171 in the High Court and in *Merck & Co Inc v Arrow Pharmaceuticals Ltd* (2006) 154 FCR 31 in the Full Court. His Honour did not accept that the French specification was incorporated by reference as a whole and for all purposes into the specification in suit but only sufficiently to understand the reference to the racemic compound in the specification in suit. Even if the French specification were incorporated as a whole, his Honour said it would take the matter no further than his decision on novelty. Spirit says that this aspect of his Honour's reasoning is an acceptance that, if the French prior art patent were incorporated by reference as a whole, his Honour accepted that at least claims 1, 10 and 11 would be invalid on the ground that they did not define a manner of manufacture.

184 Apotex's submission that the claims of the Patent do not define a manner of manufacture is based on the effect of the reference to the French prior art patent which, it submits, is then incorporated by reference. As a result, Apotex says, there is no invention which is new or inventive on the face of the specification of the Patent.

185 The French prior art patent discloses PCR 4099, the racemic mixture from which the d-enantiomer the subject of the claims of the Patent is obtained. It is also in the French prior

art patent that the activity of platelet aggregation inhibition is disclosed. Apotex says that the French prior art patent:

- Discloses both enantiomers, as well as the racemic mixture – indeed, it claims them as part of the invention;
- Discloses the particular salts of those enantiomers which are the subject of the claims in the Patent, and claims them as part of the invention;
- Discloses the therapeutic effect of the enantiomers, in inhibiting blood-platelet aggregation and thrombosis;
- Discloses that the derivatives (including the enantiomers) are well-tolerated, exhibit low toxicity and are useful; and
- Discloses and claims pharmaceutical ('*therapeutic*') compositions containing them.

186 Apotex and Spirit submit that the primary judge erred in failing to find that the specification of the French prior art patent (the French patent application referred to in the Patent was granted without amendment as the French prior art patent) was incorporated by reference for the purposes of considering the question of whether the claims of the Patent involved a manner of new manufacture on the face of the specification.

187 Apotex then points to the fact that the specification of the Patent says that the salts of the d-enantiomer were prepared in a standard manner, as the primary judge accepted.

188 Apotex submits that it follows from the disclosures in the French prior art patent and in the specification that there is no "new" or "inventive" invention on the face of the specification and that the product claims (claims 1, 2 to 5, 10 and 11) do not define a manner of new manufacture.

189 The submissions of Apotex and Spirit seem to assume that, if the French prior art patent were wholly incorporated by reference, it follows that there is no manner of new manufacture demonstrated in the specification of the Patent, This seems to be because the French prior art patent discloses derivative No 1, the racemic mixture PCR 4099 and its preparation, together with the disclosure and claim to the enantiomers of, *inter alia*, that compound. Apotex and Spirit then rely on admissions in the specification of the Patent and findings of the primary judge that the method of preparation of the d-enantiomer was routine, as were the methods of salt formation. Spirit also makes reference to the fact that the primary judge found that, '[o]*n any view*', derivative No 1, the first example in the French prior art patent, was expressly disclosed as one of the most promising of the compounds described in and exemplified in that patent.

190 The specification of the Patent acknowledges that the racemic mixture corresponding to the formula of the compound of the invention, which formula encompasses the racemic mixture and the d- and l-enantiomers, was described in the French prior art patent. The specification also states that, in an unexpected manner, of the two

enantiomers, only the d-enantiomer exhibits platelet aggregation inhibiting activity and, moreover, the inactive l-enantiomer is less well-tolerated. It is for that reason, impliedly, that the patentee continued to develop the addition salts of the d-enantiomer and pharmaceutical compositions. The description in the specification concludes with the statement that, on account of *'its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders'*.

191 The French prior art patent also reported the activity of the derivatives and their inhibiting activity on platelet aggregation and anti-thrombotic action as well as toxicological and pharmacological data that demonstrated the low toxicity of the compounds. While the enantiomers were disclosed and claimed, no distinction was drawn between the activity and toxicity of those enantiomers or between the enantiomers and the racemate. That awaited the work set out in the Patent. The results were described as *'unexpected'* and led to the claims directed to one of the enantiomers and the demonstration that the other enantiomer was not active.

192 Accepting that the French prior art patent was incorporated wholly into the Patent for the purpose of assessing whether, on its face, the Patent disclosed a manner of manufacture, in our opinion it cannot be said that the Patent failed to do so. It is not apparent from the face of the

specification that the necessary quality of inventiveness is absent.

CONCLUSION

193 It follows that:

- In respect of claim 1, to the extent that the claim is to the d-enantiomer, claim 1 is invalid on the ground of lack of novelty but, to the extent that the claim is to the pharmaceutically acceptable salts of the d-enantiomer, claim 1 is novel.
- The subject matter of claims 2 to 5 are novel.
- The subject matter of claims 10 and 11 are invalid on the ground of lack of novelty.
- The subject matter of claims 1, 2 to 5, 6 to 9, 10 and 11 are invalid on the ground of lack of inventive step.
- The subject matter of claims 1, 2 to 5, 10 and 11 do define a manner of manufacture.

194 The parties have asked that the question of costs be deferred until after the Court has published its reasons. The parties should submit proposed orders to give effect to these reasons and considerations, including any directions necessary for the resolution of any question of costs.

I certify that the preceding one hundred and fifty-four (154) numbered paragraphs are a true copy of the Reasons for Judgment herein of the Honourable Justices Bennett and Middleton.

Associate: /s/

Dated: 29 September 2009

Counsel for Apotex Pty Ltd:	Mr DK Catterns QC with Mr C Dimitriadis and Ms JM Beaumont
Solicitor for Apotex Pty Ltd:	Blake Dawson
Counsel for Spirit Pharmaceuticals Pty Ltd:	Mr SCG Burley SC with Mr JS Cooke
Solicitor for Spirit Pharmaceuticals Pty Ltd:	Blake Dawson
Counsel for Sanofi-Aventis, Sanofi-Aventis US LLC and Bristol-Myers Squibb Investco LLC:	Mr RC Macaw QC with Ms CL Cochrane
Solicitor for Sanofi-Aventis, Sanofi-Aventis US LLC and Bristol-Myers Squibb Investco LLC:	Allens Arthur Robinson
Date of Hearing:	16-19 February 2009
Date of Judgment:	29 September 2009

MOTION FILED
AUG 27 2009
138

(3)

No. 09-117

In The Supreme Court of the United States

APOTEX, INC. AND APOTEX CORP.,
Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,
Respondents.

On Petition For Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

MOTION FOR LEAVE TO FILE BRIEF *AMICI CURIAE* AND BRIEF OF AARP, PATIENTS NOT PATENTS, AND THE PUBLIC PATENT FOUNDATION AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

STACY CANAN
(Counsel of Record)
AARP FOUNDATION
MICHAEL SCHUSTER
AARP
601 E Street, NW
Washington, DC 20049
(202) 434-2060

KATHERINE J. STRANDBURG
Professor of Law
NEW YORK UNIVERSITY
SCHOOL OF LAW
40 Washington Square South
New York, NY 10012
(212) 998-2629

DAVID A. BALTO
JASON W. MCELROY
LAW OFFICE OF
DAVID A. BALTO
1350 I Street NW, #850
Washington, DC 20005
(202) 789-5424

(Additional Counsel Listed on Inside Cover)

DANIEL B. RAVICHER
THE PUBLIC PATENT
FOUNDATION, INC.
BENJAMIN N. CARDOZO
SCHOOL OF LAW
55 Fifth Avenue @
12th Street
New York, NY 10003
(212) 796-0570

JEFFREY L. LIGHT
PATIENTS NOT PATENTS
1712 I Street, NW # 915
Washington, DC 20006
(202) 277-6213

Counsel for *Amici Curiae*

MOTION FOR LEAVE TO FILE BRIEF *AMICI CURIAE*

Pursuant to Rule 37.2(b) of the Rules of the Supreme Court of the United States, *Amici* AARP, Patients Not Patents, and the Public Patent Foundation hereby request leave to file the accompanying *amicus curiae* brief. This brief is submitted in support of the petition for writ of certiorari to the Court of Appeals for the Federal Circuit. Petitioners Apotex, Inc. and Apotex Corp. have consented to the filing of this brief. Respondents Sanofi-Synthelabo, Sanofi-Synthelabo Inc., and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership received timely notice but have not consented.

INTEREST OF *AMICI CURIAE*

Amicus AARP is a nonpartisan, nonprofit membership organization addressing the needs and interests of older Americans. AARP works at the state and federal levels for legislation beneficial to its constituents, and believes that this case poses an important question for consumer access to generic drugs.

Amicus Patients Not Patents, Inc. ("PNP") is a 501(c)(3) nonprofit organization based in Washington, D.C., dedicated to ensuring greater access to healthcare. PNP believes this case could affect the cost and availability of many important medicines.

Amicus Public Patent Foundation ("PUBPAT") at Benjamin N. Cardozo School of Law is a not-for-profit legal services organization representing the public interest in the patent system, and supports

this petition to maintain patent policy within the ambit of this Court's decisions.

REASONS FOR GRANTING MOTION

Amici Curiae respectfully submit this brief in support of petitioners Apotex, Inc. and Apotex Corp. (collectively, "Apotex"), encouraging the grant of a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit, because that judgment stems from the application of an "obvious to try" approach that is inconsistent with this Court's approach to obviousness in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), and with both health and patent policy. Allowing patents on obvious improvements to existing drugs and medical treatments burdens the public with excessive health care costs, delays generic entry longer than intended by Congress, and dulls incentives for real innovation in medical care.

August 27, 2009

Respectfully submitted,

STACY CANAN
(Counsel of Record)
AARP FOUNDATION
MICHAEL SCHUSTER

AARP
601 E Street, NW
Washington, DC 20049
(202) 434-2060

Counsel for *Amici Curiae*

TABLE OF CONTENTS

MOTION FOR LEAVE TO FILE BRIEF *AMICI CURIAE* M1

REASONS FOR GRANTING MOTION M2

TABLE OF AUTHORITIES iii

INTEREST OF *AMICI CURIAE* 1

REASONS FOR GRANTING THE WRIT 4

I. THE FEDERAL CIRCUIT'S RELIANCE ON "UNEXPECTED RESULTS" TO HOLD PATENT CLAIMS NONOBVIOUS EVEN WHEN THEY RESULT FROM "OBVIOUS TO TO TRY" RESEARCH IS INCOMPATIBLE WITH THIS COURT'S OPINION IN *KSR*, CONTRARY TO STATUTE, AND INCONSISTENT WITH PATENT POLICY 4

II. THE HINDSIGHT APPROACH TAKEN TO THE "OBVIOUS TO TRY" ISSUE IN PHARMACEUTICAL CASES HAS GRAVE CONSEQUENCES FOR MILLIONS OF PERSONS 10

III. THIS CASE IS AN EXCELLENT VEHICLE FOR CLARIFYING THAT OBVIOUSNESS SHOULD BE EVALUATED WITHOUT ENGAGING IN AN EX POST INQUIRY INTO THE SPECIFIC UNPREDICTABLE OUTCOME OF AN OBVIOUS INVENTIVE ENDEAVOR 14

CONCLUSION 16

TABLE OF AUTHORITIES

Abbott Labs v. Sandoz, Inc.,
544 F.3d 1341 (Fed. Cir. 2008) 8

Abbott Labs v. Teva Pharms. USA, Inc.,
432 F. Supp. 2d 408 (D. Del. 2006) 13

Bayer Schering Pharma AG v. Barr Labs, Inc., 2009 U.S. App. LEXIS 17372 (Fed. Cir. Aug. 5, 2009) 15

Diamond v. Chakraborty,
447 U.S. 303 (1980) 8

Graham v. John Deere Co.,
383 U.S. 1 (1966) 3, 4, 5, 8

In re Deuel,
51 F.3d 1552 (Fed. Cir. 1995) 7

In re Kahn,
441 F.3d 997 (Fed. Cir. 2006) 5

In re O'Farrell,
853 F.2d 894 (Fed. Cir. 1988) 6, 7

In re Rouffet,
149 F.3d 1350 (Fed. Cir. 1998) 5

KSR Int'l Co. v. Teleflex, Inc.,
550 U.S. 398 (2007) ..... *passim*

Mandel Bros., Inc. v. Wallace,
335 U.S. 291 (1948) 7

Para-Ordnance Mfg. v. SGS Importers Int'l,
73 F.3d 1085 (Fed. Cir. 1995) 5

Takeda Chem. Indus., Ltd. v.
Alpha-pharm Pty., Ltd.,
492 F.3d 1350 (Fed. Cir. 2007) 8

Uniroyal, Inc. v. Rudkin-Wiley Corp.,
837 F.2d 1044 (Fed. Cir. 1988) 5

W.L. Gore & Assocs. v. Garlock, Inc.,
721 F.2d 1540 (Fed. Cir. 1983) 5

STATUTES

35 U.S.C. §103 ..... 5, 9, 15

OTHER AUTHORITIES

AARP, Rx Watchdog Report, April 2009,
Vol. 6, Issue 3 2

Dana Gelb Safran et al., *Prescription Drug Coverage and Seniors: Findings from a 2003 Survey*, Health Affairs (Web Exclusive) 157-58 (April 19, 2005) 11

David J. Gross et al., AARP Public Policy Institute, *Rx Watchdog Report: Trends in Manufacturer Prices of Brand Name Prescription Drugs Used by Medicare Beneficiaries 2002 to 2007*
(March 2008) 11

Dennis Kvesic, *Product Life Cycle Management: Marketing Strategies for the Pharmaceutical Industry*, 8 J. Med. Mktg. 293 (Sep. 1, 2008) 12, 13

Families USA, Cost Overdose: Growth in Drug Spending for the Elderly, 1992-2010 (July 2000) 2

Kathleen Jaeger, President & Chief Executive Officer, Generic Pharm. Ass'n, Testimony Before the U.S. House of Representatives' Energy and Commerce Committee (May 18, 2005) 10

Herbert Hovenkamp et al., IP and Antitrust: An Analysis of Antitrust Principles Applied to Intellectual Property Law § 12.5 (Supp. 2007) 12

Jan Blustein, *Drug Coverage and Drug Purchases by Medicare Beneficiaries with Hypertension*, 19 Health Affairs 219 (2000) 11

Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 Colum. L. Rev. 1471 (2008) 12

Jon Leibowitz, Chairman, Fed. Trade Comm'n, "Pay for Delay" Settlement in the Pharmaceutical Industry: How Congress Can Stop Anticompetitive Conduct, Protect Consumers' Wallets, and Help Pay for Health Care Reform (The $35 Billion Solution) (June 23, 2009) 12, 16

Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 Stan. Tech. L. Rev. 2 (2007) 14

M. Agrawal & N. Thakkar, *Surviving Patent Expiration: Strategies for Marketing Pharmaceutical Products*, 6 J. Prod. & Brand Mgmt. 305 (1997) 13

M. Burton & K. Sloper, *The Art of Using Secondary Patents to Improve Protection*, 3 Int'l J. Med. Mktg. 226 (2003) 13

Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. Rev. 63 (2004) 13

More Studies Find More Savings if Seniors Use Generic Drugs, SeniorJournal.com (March 3, 2006) *available at* http://www.Seniorjournal.com/NEWS/MedicareDrugCards/6-03-03-MoreStudiesFind.htm 11

Press Release, Generic Pharm. Assoc., Generic Pharmaceuticals Saved $734 Billion over Last Decade (May 7, 2009) 11

INTEREST OF THE *AMICI CURIAE*[1]

Amici Curiae AARP, Patients Not Patents, and the Public Patent Foundation respectfully submit this brief in support of petitioners Apotex, Inc. and Apotex Corp. (collectively, "Apotex"), encouraging the grant of a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit, because that judgment stems from the application of an "obvious to try" approach that is inconsistent with this Court's approach to obviousness in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), and with both health and patent policy. Allowing patents on obvious improvements to existing drugs and medical treatments burdens the public with excessive health care costs, delays generic entry longer than intended by Congress, and dulls incentives for real innovation in medical care.

Amicus AARP is a nonpartisan, nonprofit membership organization of nearly 40 million persons age 50 or older. It is dedicated to addressing the needs and interests of older Americans. As the country's largest membership organization, AARP has a long history of advocating for access to affordable health care and for controlling costs without compromising quality. Affordable prescription

---

[1] No counsel for a party authored this brief in whole or in part and no person, other than *amici*, their members, or counsel made a monetary contribution to the preparation or submission of this brief. Counsel of record for all parties received notice at least 10 days prior to the due date of the amici's intention to file this brief. Petitioners have consented to the filing of this brief. A Motion For Leave to File *Amici's* Brief is included herein.

medication is particularly important to the older population which, because of its higher rates of chronic and serious health conditions, has the highest rate of prescription drug use. Persons over sixty-five, although only thirteen percent of the population, account for thirty-four percent of all prescriptions dispensed and forty-two cents of every dollar spent on prescription drugs. Families USA, Cost Overdose: Growth in Drug Spending for the Elderly, 1992-2010 at 2 (July 2000). Since prescription drug spending has skyrocketed over the last decade and a half, and national health expenditures on prescription drugs have quadrupled, AARP advocates for broader access to prescription drugs and lower prescription drug costs for consumers. To that end, AARP works at the state and national levels for laws and policies that will bring more generic competition to the marketplace. *See e.g.*, AARP, Rx Watchdog Report, April 2009, Vol. 6, Issue 3, available at http://assets.aarp.org/www.aarp.org_/cs/health/rx_watchdog_apr09.pdf.

Amicus Patients Not Patents, Inc. ("PNP") is a 501(c)(3) nonprofit organization based in Washington, D.C. PNP is committed to ensuring access to healthcare through litigation, advocacy and education. PNP is organized around the principle that medical treatment should not be denied or restricted because of the existence of patents or other intellectual property barriers. PNP has successfully challenged the validity of patents on drugs owned by pharmaceutical companies through administrative proceedings at the U.S Patent and Trademark Office. PNP supports a grant of certiorari in this case because the outcome will affect the cost and availability

of the drug clopidogrel and of other important medicines.

Amicus Public Patent Foundation ("PUBPAT") at Benjamin N. Cardozo School of Law is a not-for-profit legal services organization that represents the public interest in the patent system, and most particularly the public interest in protecting against the harms caused by undeserved patents and unsound patent policy. PUBPAT provides the general public and specific persons or entities otherwise deprived of access to the patent system with representation, advocacy, and education. PUBPAT has argued for sound patent policy before this Court, the Court of Appeals for the Federal Circuit, various district courts, the United States House of Representatives, the United States Patent and Trademark Office (USPTO), the United Nations, the European Union Parliament, and other judicial, governmental and political bodies. PUBPAT has also requested that the USPTO re-examine specifically identified undeserved patents causing significant harm to the public. The USPTO has granted each such request. These accomplishments have established PUBPAT as a leading provider of public service patent legal services and one of the loudest voices advocating for comprehensive patent reform. PUBPAT supports this petition for certiorari because of its interest in ensuring that the obviousness bar to patentability is maintained at a proper level consistent with *KSR, Graham v. John Deere Co.*, 383 U.S. 1 (1966), and this Court's other decisions.

REASONS FOR GRANTING THE WRIT

I. THE FEDERAL CIRCUIT'S RELIANCE ON "UNEXPECTED RESULTS" TO HOLD PATENT CLAIMS NONOBVIOUS EVEN WHEN THEY RESULT FROM "OBVIOUS TO TRY" RESEARCH IS INCOMPATIBLE WITH THIS COURT'S OPINION IN *KSR*, CONTRARY TO STATUTE, AND INCONSISTENT WITH PATENT POLICY

As this Court reaffirmed only two years ago, the nonobviousness requirement is intended to ensure that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR v. Teleflex,* 550 U.S. 398, 427 (2007). Patents are awarded as "an inducement, to bring forth new knowledge." *Graham v. John Deere Co.*, 383 U.S. 1, 9 (1966). Thus, patents granted on "advances that would occur in the ordinary course without real innovation retard[] progress," *KSR*, 550 U.S. at 419, and impose the costs of exclusivity on the public needlessly. When unnecessary patent protection delays the introduction of generic drugs, the burden on the public is not only financial; there are dire implications for those suffering from disease and other health problems. Therefore it is particularly important that the lower courts consistently and correctly apply the patentability standard set out in the statute and in this Court's precedents.

To distinguish inventions that would be made in the ordinary course from those requiring a patent incentive, section 103 of the Patent Act requires that obviousness be evaluated according to the perspective of a "person having ordinary skill in the art"

("PHOSITA") and that that perspective be applied "at the time the invention was made." 35 U.S.C. § 103. Importantly, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." 550 U.S. at 421.

Both this Court and the Federal Circuit have long recognized that it is important to focus on the state of the art at the time an invention was made so as to avoid the hindsight bias that may result from an ex post perspective on the invention. *KSR*, 550 U.S. at 421; *Graham*, 383 U.S. at 36 (1966); *In re Kahn*, 441 F.3d 997, 986 (Fed. Cir. 2006); *Para-Ordnance Mfg. v. SGS Importers Int'l*, 73 F.3d 1085, 1087-88 (Fed. Cir. 1995); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir. 1988); *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1551–53 (Fed. Cir. 1983). In fact, the Federal Circuit's "teaching, suggestion, or motivation to combine" test was an attempt to combat the propensity to underestimate the nonobviousness of inventions that appear simple once they have been made. *KSR*, 550 U.S. at 418–19; *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Though the Federal Circuit's rigid application of the test was an erroneous means to deal with the risk of hindsight bias, *KSR*, 550 U.S. at 419, this Court acknowledged the concern that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *Id.* at 421.

Though the Federal Circuit recognizes the danger that a nonobvious invention might appear

obvious in retrospect, its obviousness doctrine ignores the complementary danger that an *obvious* invention might appear *nonobvious* in retrospect when desirable properties of the invention are revealed only after the fact. There are numerous situations, particularly in the pharmaceutical and chemical arenas, in which the specific outcome of a particular research direction is not predictable in advance. In many of these cases it is nonetheless perfectly clear to a person having ordinary skill in the art both how to proceed and that the research is likely to produce worthwhile results. In other words, it may be "obvious to try" a specific research path in light of the reasonable probability of a useful outcome, even when the exact parameters of the outcome are not known in advance. *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

In the instant case, for example, there was no way to predict exactly how the properties of the right and left enantiomers of PCR4099 would differ in toxicity and effectiveness, yet it was well known to the PHOSITA that there were likely to be differences of pharmaceutical significance and that there were well-known techniques available for separating the enantiomers. Thus, even though the PHOSITA would not have known just how good a blood thinner clopidogrel would turn out to be, there were strong incentives to pursue the well-defined research path to separate the enantiomers and determine their differential properties. The surprisingly good properties of clopidogrel would thus have been uncovered in the ordinary course of the PHOSITA's research.

As this Court recognized in *KSR*, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 550 U.S. at 421. Indeed, the Federal Circuit long ago recognized this possibility, *O'Farrell*, 853 F.2d at 903-04, as did this Court, *Mandel Bros., Inc. v. Wallace*, 335 U.S. 291, 296 (1948) ("skillful experiments in a laboratory, in cases where the principles of the investigations are well known, and the achievement of the desired end requires routine work rather than imagination, do not involve invention"). Prior to *KSR*, however, a line of Federal Circuit cases had lost track of this reality, stating categorically that an invention could not be proved obvious by demonstrating that it was "obvious to try." *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995), for example, opined that "obvious to try has long been held not to constitute obviousness" and that "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *Id.*

In *KSR*, this Court repudiated this categorical approach, making it clear that there are situations in which the fact that it is "obvious to try" a particular development can demonstrate obviousness under the Patent Act. 550 U.S. at 421. Since *KSR* was decided, however, confusion has reigned in the Federal Circuit's "obvious to try" jurisprudence, as detailed in the Petition for Certiorari in this case. Opinions have continued to focus, incorrectly, on an ex post analysis of the properties of a claimed invention, rather than

on whether the invention would have been made in the ordinary course without the need for a patent incentive. *See, e.g., Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1351 (Fed. Cir. 2008); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361–62 (Fed. Cir. 2007) (discussing how Alphapharm's obviousness argument would fail on either of two grounds, one that claimed compound possessed unexpected qualities post-modification). In this case, the Federal Circuit and district courts relied heavily on the "unexpected and unpredictable properties of clopidogrel [the right-handed enantiomer]" in holding that the separated enantiomer was nonobvious. Pet. App. at 27a–28a, 109a, 111a. .

As demonstrated in the opinion in this case, the Federal Circuit routinely relies on unexpected results to rebut what it calls a "prima facie case of obviousness." Pet. App. at 105a–106a. This focus on unanticipated properties of an invention directly conflicts with the statutory requirement that obviousness be evaluated at the time of invention and with this Court's recognition in *KSR* that the patent laws are not intended to award exclusive rights to "the results of ordinary innovation." 550 U.S. at 427.

Patents are intended to provide incentives for inventive efforts. *Diamond v. Chakrabarty*, 447 U.S. 303, 307 (1980); *Graham*, 383 U.S. at 687-88. The nonobviousness requirement helps to ensure that patents are available only when they are needed to provide such incentives. *KSR*, 550 U.S. at 427. Results that are unanticipated can have no effect on such ex ante incentives and thus should play no part in evaluating obviousness. If a particular course of

action is sufficiently motivated by "design need or market pressure" and there is a reasonable expectation of a successful outcome to the project, the fact that the results of the project turn out to be even better than the PHOSITA would have anticipated is simply immaterial to the evaluation of obviousness "at the time of the invention." 35 U.S.C. § 103.

The inquiry into whether a particular research path would have been obvious to try in light of "ordinary skill and common sense," *KSR*, 550 U.S. at 421, does not run afoul of the statutory caveat that "patentability shall not be negatived by the manner in which the invention was made," 35 U.S.C. § 103, regardless of whether the claimed invention has unexpected properties. The question is whether the research would have been obvious to try *to the PHOSITA* at the time of the invention. The manner in which a particular patent applicant produced the claimed invention is irrelevant.

In this case, Apotex correctly argued that "the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties." Pet. App. at 27a-28a. The Federal Circuit mistakenly rejected this argument in favor of a focus on the irrelevant determination that "[t]he evidence at trial well supported the finding that the result of this separation of enantiomers was unpredictable." *Id.* at 30a. This emphasis on an ex post facto inquiry into the outcome of the research, rather than on the need for patent incentives to engage in it, has alway

been inconsistent with the statutory focus on the time of the invention. After this Court's opinion in *KSR*, the approach is untenable.

II. THE HINDSIGHT APPROACH TAKEN TO THE "OBVIOUS TO TRY" ISSUE IN PHARMACEUTICAL CASES HAS GRAVE CONSEQUENCES FOR MILLIONS OF PERSONS.

The non-obviousness standard for patent approval is crucial in the context of pharmaceuticals and consumer access to life-saving drugs. Relying on the unpredictability of the results to award patents for the fruit of obvious research paths will lead to unwarranted patent protection for obvious pharmaceutical advances, sacrificing access to important medicines without a compensating increase in innovation. Because results that can be characterized as unpredictable in some way are so common in the pharmaceutical field, such a hindsight-driven analysis vastly and unnecessarily expands the scope of patentability, directly harming consumers through reduced access, higher prices, and restrained competition. This excessive patenting also leads to patients foregoing needed medical care to save money, damaging the public health of the nation.

Generic drugs cost, on average, 70% less than branded drugs, and yielded $734 billion dollars in savings to consumers between 1998 and 2009.[2]

---

[2] *See* Kathleen Jaeger, President & Chief Executive Officer, Generic Pharm. Ass'n. Testimony Before the U.S. House of Representatives' Energy and Commerce Committee (May 18, 2005) *available at* www.gphaonline.org/resources/2009/02/12/

Studies have shown that Medicare recipients in particular could save substantial sums by using more generic drugs.[3] These statistics demonstrate the huge financial stakes at issue for consumers regarding the availability of generic pharmaceuticals. Even more significantly, research consistently has shown that patients respond to higher drug prices by reducing drug consumption: *i.e.*, "financial barriers compel older Americans to forgo needed drug treatment."[4] Further exacerbating these realities is the fact that between 2002 and 2007 annual increases in prices for branded pharmaceuticals have outpaced inflation by a factor as high as 3.[5] When drugs are unnecessarily expensive, the public health is undermined.

---

gpha-testimony-house-energy-and-commerce-committee-generic-utilization; Press Release, Generic Pharm. Ass'n, Generic Pharmaceuticals saved $734 Billion over Last Decade (May 7, 2009) *available at* www.gphaonline.org/media/press-releases/2009/generic-pharmaceuticals-saved-734-billion-over-last-decade.

[3] *See* More Studies Find More Savings if Seniors Use Generic Drugs, SeniorJournal.com (March 3, 2006) *available at* http://www.seniorjournal.com/NEWS/MedicareDrugCards/6-03-03-MoreStudiesFind.htm.

[4] Jan Blustein, *Drug Coverage and Drug Purchases by Medicare Beneficiaries with Hypertension*, 19 Health Affairs 219, 228 (2000) *available at* http://content.healthaffairs.org/cgi/reprint19/2/219; Dana Gelb Safranet al., Prescription Drug Coverage and Seniors: Findings from a 2003 Survey, Health Affairs (Web Exclusive) 157-58 (Apr. 19, 2005) *available at* http://content.healthaffairs.org/cgi/reprint/hlthaff.w5.152v1.

[5] David J. Gross et al., AARP Public Policy Institute, *Rx Watchdog Report: Trends in Manufacturer Prices of Brand Name Prescription Drugs Used by Medicare Beneficiaries 2002 to 2007* at iv (March 2008) *available at* http://assets.aarp.org/

The "obvious to try" doctrine at issue in this case is particularly important because pharmaceutical companies have increasingly used patents on incremental modifications or reformulations of existing drugs to extend their market exclusivity beyond the generous protections already available to them via patent protection on the basic drug, patent term extensions under the Hatch-Waxman Act, and data exclusivity periods provided by the FDA.[6] For example, more than one-third of products launched from 2002 to 2005 by the top fifty pharmaceutical manufacturers were reformulations of drugs already under patent, for which the "obvious to try" issue has particular salience. Dennis Kvesic, *Product Life Cycle Management: Marketing Strategies for the Pharmaceutical Industry*, 8 J. of Med. Mktg. 293, 296 (Sep. 1, 2008). This problem has engendered high-profile antitrust litigation accusing pharmaceutical companies of attempting to defeat generic penetration through anticompetitive manipulations of drug

---

rgcenter/health/2008_05_watchdog_q407.pdf.

[6] *See* Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 Colum. L. Rev. 1471 (2008) (analyzing tactics used by pharmaceutical companies to extend product life by using reformulations of previously existing drugs); Herbert Hovenkamp et al., IP and Antitrust: An Analysis of Antitrust Principles Applied to Intellectual Property Law § 12.5 (Supp. 2007) (same); Jon Leibowitz, Chairman, Fed. Trade Comm'n, "Pay for Delay" Settlements in the Pharmaceutical Industry: How Congress Can Stop Anticompetitive Conduct, Protect Consumers Wallets, and Help Pay for Health Care Reform (The $35 Billion Solution) (June 23, 2009) *available at* http://www.ftc.gov/speeches/leibowitz/090623payfordelayspeech.pdf (describing problems caused by reverse payment settlements to keep generic drugs off the market).

formulations. *See Abbot Labs v. Teva Pharms. USA, Inc.*, 432 F. Supp. 2d 408 (D. Del. 2006).

When such a large fraction of "new" drugs hitting the market are reformulations of previously launched drugs, the Federal Circuit's erroneous application of the obvious to try doctrine leads directly to consumers foregoing needed medical attention and over-paying for health care.

These uses of patents on incremental and "obvious to try" advances, known to critics as "evergreening," Mark A. Lemley and Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U.L. Rev. 63, 82-83 (2004) and promoted by marketers as "product life cycle management,"[7] are attempts to game the system to provide windfall profits to pharmaceutical patent holders at the expense of the public health. The failure of some Federal Circuit panels to follow *KSR*'s directive that the obviousness requirement must provide incentives for innovation over and above what would occur in the ordinary course of a competitive marketplace, 550 U.S. at 417, will only lead to more gamesmanship on the part of patent owners.

---

[7] *See, e.g.*, Dennis Z. Kvesic, *Product Lifecycle Management: Marketing Strategies for the Pharmaceutical* Industry, 8 J. Med. Mktg. 293 (2008) (describing successful use of secondary patents to extend profit timeline of drugs soon to expire); M. Burton & K. Sloper, *The Art of Using Secondary Patents to Improve Protection*, 3 Int'l J. of Med. Mktg. 226 (2003) (same); M. Agrawal & N. Thakkar, *Surviving Patent Expiration: Strategies for Marketing Pharmaceutical Products*, 6 J. Prod. & Brand Mgmt. 305 (1997) (same).

III. THIS CASE IS AN EXCELLENT VEHICLE FOR CLARIFYING THAT OBVIOUSNESS SHOULD BE EVALUATED WITHOUT ENGAGING IN AN EX POST INQUIRY INTO THE SPECIFIC UNPREDICTABLE OUTCOME OF AN OBVIOUS INVENTIVE ENDEAVOR.

This case is an excellent vehicle for this Court's consideration of the "obvious to try" issue. The particular context of enantiomer patenting is important and recurring, while also representative of a larger concern in fields such as chemistry, in which the properties of a new product are often known only after it has been made. A large fraction of drugs are made of chiral molecules and the potential for improved effectiveness and lower toxicity in single enantiomer drugs has long been well known. Indeed a 1998 study found that half of a sample of over one thousand drugs under development were single enantiomer drugs.[8] The development of a single enantiomer drug is thus a particularly clear example of an obvious to try research path with unpredictable results: one of two enantiomers will often have more desirable properties, yet testing is required to determine which one and how much more desirable the properties will be.

---

[8] *See* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 Stan. Tech. L. Rev. 2, available at http://stlr.stanford.edu/pdf/darrow-patentability.pdf, for an extensive discussion of the importance of chiral and single enantiomer drugs and their patentability just prior to *KSR*.

We now stand more than two years after this Court issued its opinion in *KSR*. Nevertheless, decisions, such as the one at issue here, continue to turn on a hindsight consideration of unexpected properties rather than on whether, at the time of the invention, the claimed invention was within the grasp of the person of ordinary skill in the art. Federal Circuit case law on the important "obvious to try" issue remains inconsistent, with significant disagreement among the judges. For example, in a case decided while this brief was being written, the majority found a reformulation of an existing drug "obvious to try" over a dissent from the judge who wrote the opinion below in the present case. The majority reasoned that at the time of the invention "a person having ordinary skill in the art ha[d] reached a crossroads where he must choose between two known options," and identified that situation with *KSR*'s "finite number of identified, predictable solutions." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 2009 U.S. App. LEXIS 17372 (Fed. Cir. August 5, 2009) at *21, *citing KSR*, 550 U.S. at 421.

Now that *KSR* has swept away the categorical rule against "obvious to try" evidence and argument, there is an urgent need for this Court to step in and clarify that post hoc evidence of unexpected results has no role to play in evaluating whether a course of action was sufficiently "obvious to try" to render its results unpatentable under section 103 of the Patent Act.

CONCLUSION

For the foregoing reasons, the petition for writ of certiorari should be granted.

August 27, 2009

Respectfully submitted,

Stacy Canan
(Counsel of Record)
AARP Foundation
Michael Schuster
AARP
601 E Street, NW
Washington, DC 20049
(202) 434-2060

David A. Balto
Jason W. McElroy
Law Office of
David A. Balto
1350 I Street NW, #850
Washington, DC 20005
(202) 789-5424

Katherine J. Strandburg
Professor of Law
New York University
School Of Law
40 Washington Square
So.
New York, NY 10012
(212) 998-2629

Daniel B. Ravicher
The Public Patent
Foundation, Inc.
Benjamin N. Cardozo
School of Law
55 Fifth Avenue @
12th Street
New York, NY 10003
(212) 796-0570

Jeffrey L. Light
Patients Not Patents
1712 I Street, NW #915
Washington, DC 20006
(202) 277-6213

Counsel for Amici Curiae